UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE MEDICINA
Departamento de Medicina

TESIS DOCTORAL

Demencia :estados preclínicos y mortalidad en cohortes suecas

Dementia : preclinical stages and mortality in Swedish cohorts

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Sara García Ptacek

Directores

Maria Eriksdotter
María Luz Cuadrado Pérez

Madrid, 2015

UNIVERSIDAD COMPLUTENSE DE MADRID
DEPARTAMENTO DE MEDICINA

DEMENCIA: ESTADIOS PRECLÍNICOS Y MORTALIDAD EN COHORTES SUECAS

DEMENTIA: PRECLINICAL STAGES AND MORTALITY IN SWEDISH COHORTS

TESIS DOCTORAL / PhD THESIS

Sara García Ptacek

DIRECTORAS / SUPERVISORS:

Prof. Maria Eriksdotter
Department of Neurobiology, Care sciences and Society
Karolinska Institutet, Stockholm, Sweden
Prof. María Luz Cuadrado Pérez
Department of Medicine
Universidad Complutense de Madrid, Madrid, Spain

THIS THESIS IS IN PART BASED ON THE FOLLOWING PEER-REVIEWED PAPERS, WHICH ARE REFERRED TO IN THE TEXT AS I-III

I. Garcia-Ptacek S, Cavallin L, Kåreholt I, Kramberger MG, Winblad B, Jelic V, Eriksdotter M. **Subjective cognitive impairment: who are they? SCI subjects in our clinical practice.** Dement Geriatr Cogn Dis Extra accepted for publication, *in press.*

……

II. Garcia-Ptacek S, Farahmand B, Kåreholt I, Religa D, Cuadrado ML, Eriksdotter M**. Mortality risk after dementia diagnosis by dementia type and underlying factors: a cohort of 15209 patients based on the Swedish Dementia Registry.** J Alzheimers Dis 2014;41:467-77.

……

III. García-Ptacek S, Kåreholt I, Farahmand B, Cuadrado ML, Religa D, Eriksdotter M. **Body-mass index and mortality in incident dementia: a cohort study on 11,398 patients from SveDem, the Swedish Dementia Registry.** J Am Med Dir Assoc 2014;15:447.e1-7.

ACKNOWLEDGEMENTS

This doctoral thesis has been conducted at the Department of Medicine, Faculty of Medicine, Universidad Complutense de Madrid in collaboration with the Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Sweden.

Many persons and institutions have participated in this project or in the years of groundwork that preceded it: I would like to express my deepest appreciation to those who have made this journey possible.

First and foremost, my main supervisor, Professor Maria Eriksdotter for sharing your vision and inviting me to Stockholm. Your technical and moral support made this work possible. Your clarity and even temperament were much appreciated in times of stress. The Swedish word for "supervisor" is "handledare" or "she who leads by the hand". You have done precisely that, showing me new avenues of thinking without stifling my independence and creativity. Every meeting with you has enriched my work.

To Maria Luz Cuadrado, my co-supervisor, for your technical and moral support, good disposition, unquestionable dedication to my work and prompt answers to all of my questions.

Professor Bengt Winblad for lending me your kind ear, as well as for your moral and practical support, and for creating a fabulous work environment.

Assistant Professor Ingemar "Pingo" Kåreholt for your friendship, practical help after my arrival in Stockholm, and out-of-the-box thinking. Your patience in teaching me Swedish and statistics cannot be forgotten.

To the Swedish Dementia Registry, SveDem, and to all the people and institutions that participate in it. Dorota Religa, for her detailed article comments, Bahman Farahmand for statistical support, Pavla Cermakova for her attention to detail, Seyed-Mohammad Fereshtehnejad, Azadeh Karami, and Farshad Falahati for their insight and good cheer. To Ann-Katrin Edlund, Emma Timerdal and Karin Vestling, who fix problems and hold researchers to schedule. Ingrid Nilsson-Modéer, for volunteering herself for my first "supervision" experiment and working with me in SveDem. To all the

coordinators, doctors, nurses and other health professionals and governmental authorities that make SveDem possible.

To the Karolinska University Hospital in Huddinge, particularly to those in the Department of Geriatrics and the Karolinska Memory Clinic for providing the Memory Clinic database and a cheerful work environment. Vesna Jelic, Milica Kramberger, Lena Cavallin, and Daniela Enache for their work in the database and collaboration. Johan Lökk, Daas Sater, and Anders Wennlund for helping me transition into the Swedish healthcare system.

The department of Neurology at Hospital Clínico San Carlos in Madrid where I spent my residency. I am thankful to have had the opportunity to train in a top-notch institution, and have felt supported and encouraged throughout my training by all the attending neurologists and by the department head. Jesús Porta-Etessam for his mentorship. I can´t forget the nurses, nursing assistants and residents who lightened the load on busy shifts and shared their personalities and experience. I have learned from the older and younger residents and from my co-residents, Cristina Valencia Sánchez and Octavio Rodríguez Gómez: you are a brilliant bunch and I have been lucky to share this time with you. Neurology is a beautiful specialty, intricate, intriguing and changing and it is a joy to share it with all of you.

To my parents, for their love and confidence in me. Andrea, my sister, for demonstrating the properties of a *junco verde*. Anders, for his love and support.

Finally, my sincere appreciation to the Karolinska Memory Clinic and SveDem patients and caregivers, who find a way to be generous with their time and data even at a terrible time.

This research was supported financially by the Swedish Association of Local Authorities and Regions, the Swedish Brain Power network, Alzheimerfonden, Stiftelsen för Gamla Tjänarinnor, and KI foundations.

ABSTRACT

The higher percentage of individuals surviving to older ages has exponentially increased the prevalence of Alzheimer's disease (AD) and other dementias. There are 4.6 million new cases worldwide each year and the estimates suggest that prevalence will double every 20 years. Most dementia cases correspond to AD. With 50% of those 85 and above expected to develop AD, the global burden of disease has reached pandemic proportions. With no effective preventive or disease-modifying treatments yet available, the prospect for those threatened or suffering from most types of dementia remains somber. Meanwhile, the cost and social impact of these diseases escalates, especially in countries with large aging populations such as Spain and Sweden.

The neurodegenerative processes which lead to dementia span decades and are not entirely understood. Even after diagnosis, the course of the disease is extremely variable between individuals, with fluctuating and progressively worsening cognition underlying varying degrees of functional impairment. Estimates of survival after dementia diagnosis range from 3 to 15 years, and individual patient survival remains unpredictable. Previous studies suggest that type of dementia, gender, age and cognitive level, among other baseline factors, could impact prognosis. Patients and families demand knowledge on mortality after dementia diagnosis, which is also critical to public health planning. The aim of this thesis is double: first, to contribute to the characterization of patients with mild cognitive impairment (MCI) and subjective cognitive complaints (SCI) who might represent a pre-dementia stage of Alzheimer's disease. Second, once a diagnosis of dementia is established, we aim to identify those factors which contribute to mortality prognosis.

Study I was based on the clinical patient database collected at the Karolinska Memory Clinic, Karolinska University Hospital, Huddinge, Sweden, with data drawn retrospectively from clinical records.

For this study, 993 patients with a diagnosis of either AD, MCI or SCI were selected. Descriptive statistics and comparisons of characteristics between AD, MCI and SCI groups are provided. A logistic regression model (based on age, sex and cerebrospinal fluid biomarkers) was created to analyze which characteristics in the MCI and SCI groups increased their similarity to the AD population within the statistical model. First, a model was created that accurately classified AD, MCI and SCI individuals. Results from this model were used to assign a probability to each individual in the sample of being more or less "AD-like" according to the model. This probability was used as an outcome variable to determine which factors increased an SCI subject's probability of being considered "AD-like". In this study, SCI subjects were younger, with more years of formal education, higher baseline cognition; less generalized global and cortical atrophy, and less medial temporal atrophy (MTA) than the MCI or AD groups. Within the statistical regression model, markers of cardiovascular risk, confluent white matter lesions, MTA and central atrophy were identified as increasing the probability of an SCI patient to be classified as "AD-like" by the model.

Studies II and III are based on SveDem, the Swedish quality dementia registry which records incident dementia diagnosis throughout Sweden. SveDem was established in 2007 to improve quality and equality of care for dementia patients throughout the country. With coverage of more than 95% of all specialized clinics nationwide and more than 45 000 individual entries to date, it affords a unique opportunity to explore factors influencing survival after dementia diagnosis.

These two studies employed a sample from SveDem to explore factors associated with mortality risk at the time of dementia diagnosis. Study I examined 15 209 patients diagnosed in memory clinics and followed prospectively until death or end of follow-up. Higher age, male gender, lower baseline cognitive level as defined by the Mini-Mental State Examination (MMSE), institutionalization, and higher number of habitual medication taken by the patient were associated with higher mortality risk. AD presented lower risk than any other dementia disorder while vascular dementia (VaD) was the deadliest in crude analyses. After adjusting for sex, age, number of medication (as a

proxy for comorbidity) and MMSE, frontotemporal dementia (FTD) presented with the highest risk. Study II examined the relationship between body-mass index (BMI) and mortality after dementia diagnosis in 11 398 patients. Higher BMI was associated with lower mortality risk, with the highest risk appearing in the category with BMI under 18.5 kg/m^2 and the lowest risk in the obese weight category (BMI 30 kg/m^2 or above). Each point increase in BMI was associated with a reduction in mortality risk up to, and including BMI 29.9 kg/m^2 for the whole cohort and for men, and up to 24.9 kg/m^2 in women.

In conclusion, AD, MCI and SCI groups have distinct characteristics. Some clinical markers, such as atrophy or cardiovascular risk, might help identify SCI subjects at higher risk. Once a diagnosis of dementia is established, factors such as higher age, male sex, lower MMSE, non-AD dementia, comorbidity, BMI under 29.9 for men and under 24.9 for women, and institutionalization are associated with higher mortality risk.

Key words: Dementia, subjective cognitive impairment, mild cognitive impairment, Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease with dementia, mixed Alzheimer and vascular dementia, vascular dementia, epidemiology, mortality, quality registry, BMI.

RESUMEN

En las últimas décadas, el aumento de la esperanza de vida de la población ha elevado la prevalencia de la enfermedad de Alzheimer (EA) y de otras demencias de forma exponencial. Cada año 4,6 millones de personas debutan con un cuadro de demencia y se estima que la prevalencia se duplicará cada 20 años. La mayoría de los casos de demencia corresponden a EA. Con estimaciones que indican que alrededor del 50% de las personas de más de 85 años llegarán a sufrir una EA, la carga global de esta enfermedad está alcanzando proporciones pandémicas. Dado que no existen tratamientos preventivos o modificadores de la enfermedad para la mayoría de las causas de demencia, las perspectivas de la población que padece demencia o está amenazada por esta posibilidad siguen siendo sombrías. Entre tanto, el coste y el impacto social de estas enfermedades continúan creciendo, especialmente en países con poblaciones envejecidas, como Suecia y España.

En realidad las enfermedades neurodegenerativas que provocan cuadros de demencia se instauran de forma insidiosa a lo largo de muchos años, y su evolución no es del todo conocida. Incluso después del diagnóstico, el curso clínico es muy heterogéneo entre unos individuos y otros, con grados variables de deterioro funcional condicionados por el ritmo de progresión de la enfermedad y por posibles fluctuaciones. Las estimaciones de supervivencia a partir del diagnóstico de demencia oscilan entre 3 y 15 años, y la supervivencia de un paciente en concreto resulta impredecible. Los datos de algunos estudios sugieren que el tipo de demencia, el sexo, la edad y el nivel cognitivo, entre otros factores, podrían afectar a la supervivencia. Tanto los pacientes como sus familias demandan información acerca del pronóstico, y esta información es también fundamental para una correcta planificación socio-sanitaria. El objetivo de esta tesis es doble: en primer lugar, contribuir a la caracterización de los pacientes con deterioro cognitivo ligero (DCL) y quejas cognitivas subjetivas (QCS) que podrían estar en un estadio pre-demencia de la EA. En segundo lugar, una vez establecido el diagnóstico de demencia, identificar aquellos factores que pueden influir en la supervivencia.

El estudio I se centra en la base de datos de pacientes atendidos en la Unidad de Memoria del Hospital Universitario Karolinska, en Huddinge, Suecia, con datos recogidos de las historias clínicas de manera retrospectiva.

Para este estudio se seleccionaron 993 pacientes con diagnóstico de EA, DCL o SCI. Se compararon las características entre los grupos de EA, DCL y QCS, y se creó un modelo de regresión logística (basado en edad, sexo y biomarcadores en líquido cefalorraquídeo) para analizar qué características de los grupos QCS o MCI aumentaban su similitud con la muestra EA dentro del modelo. En primer lugar, se generó un modelo que clasificaba correctamente los sujetos en las categorías de EA, DCL o QCS. Los resultados de este modelo se emplearon para asignar una probabilidad a cada individuo de ser más o menos "similar a EA". Esta probabilidad se empleó como variable resultado para determinar qué factores aumentaban la probabilidad de un sujeto con QCS de ser clasificado como "similar a EA" en el modelo. En este estudio, los sujetos con QCS fueron más jóvenes, tenían más años de escolaridad, mejor cognición basal, menos atrofia global y cortical generalizada, y menos atrofia del lóbulo temporal medial que los sujetos con DCL o EA. Dentro del modelo de regresión logística, los marcadores de riesgo cardiovascular, las lesiones de sustancia blanca confluentes, la atrofia del lóbulo temporal medial y la atrofia central aumentaban la probabilidad de los pacientes con QSC de ser clasificados como "similares a EA" por el modelo.

Los estudios II y III se basan en SveDem, el registro nacional de demencia sueco, que recoge diagnósticos incidentales de demencia de todo el país. SveDem se creó en 2007 para mejorar la calidad y la equidad en el cuidado de los pacientes con demencia en Suecia. Con una cobertura de más del 95% de todos los centros especializados en memoria a nivel nacional y más de 45 000 pacientes registrados en el momento actual, SveDem representa una oportunidad única para analizar los factores que influyen en la supervivencia después del diagnóstico de demencia.

Estos dos estudios emplearon una cohorte de SveDem para analizar qué factores se asociaban con un mayor riesgo de mortalidad en el momento del diagnóstico. En el

estudio II se incluyeron 15 209 pacientes diagnosticados en centros de memoria especializados y seguidos prospectivamente hasta su muerte o el fin del estudio. La edad más avanzada, el sexo masculino, el peor nivel cognitivo basal medido por el *Mini-Mental State Exam* (MMSE), la institucionalización y el mayor consumo habitual de fármacos se asociaron con un riesgo de mortalidad más elevado. La EA presentó mejor supervivencia que otras demencias, mientras que la demencia vascular (DV) fue la más letal en análisis crudos. Tras ajustar por sexo, edad, número de fármacos y MMSE, la demencia frontotemporal (FTD) presentó el riesgo más alto.

El estudio III analizó la relación entre el índice de masa corporal (IMC) y la mortalidad después del diagnóstico de demencia en 11 398 pacientes. Las cifras más altas de IMC se asociaron con menor riesgo de mortalidad: el mayor riesgo se evidenció en el grupo con IMC inferior a 18.5 kg/m^2 y el riesgo más bajo en pacientes en el grupo con obesidad (IMC 30 kg/m^2 o superior). Cada punto de incremento en IMC se asoció con una reducción del riesgo de mortalidad hasta un IMC de 29,9 en toda la cohorte y en los varones, mientras que esta reducción se demostró sólo hasta un IMC de 24,9 en el caso de las mujeres.

En conclusión, la EA, el DCL y las QCS tienen características distintivas. Algunos marcadores clínicos, como la atrofia cerebral y los factores de riesgo cardiovascular, podrían ayudar a identificar sujetos con QCS con mayor riesgo de sufrir una EA. Una vez establecido un diagnóstico de demencia, determinados factores como la edad avanzada, el sexo masculino, la menor puntuación en el MMSE, la demencia no-EA, la comorbilidad, el IMC menor de 29,9 en varones y menor de 24,9 en mujeres y la institucionalización se asocian con mayor mortalidad.

Palabras clave: Demencia, quejas cognitivas subjetivas, deterioro cognitivo ligero, enfermedad de Alzheimer, demencia frontotemporal, demencia por cuerpos de Lewy, enfermedad de Parkinson con demencia, demencia de causa mixta Alzheimer y vascular, demencia vascular, epidemiología, mortalidad, registro de calidad, IMC.

SAMMANFATTNING

Den ökande andelen individer som överlever till hög ålder har orsakat en exponentiell ökning i prevalensen av Alzheimers demens (AD) och andra demenssjukdomar. Varje år insjuknar 4,6 miljoner personer av demens i världen och prevalensen beräknas fördubblas vart 20e år. De flesta demensfallen är AD. Femtio procent av personerna över 85 förväntas få AD. Den globala sjukdomsbördan har nått epidemiska proportioner. Utan effektiva förebyggande eller sjukdomsmodifierande behandlingar är utsikten mörk för dem som drabbas av demens. Samtidigt stiger kostnaderna och de sociala konsekvenserna av demenssjukdomarna, särskilt i länder med stor åldrande befolkning som Spanien och Sverige.

Neurodegenerativa processer som leder till demens pågår i årtionden och är inte helt klarlagda. Även efter diagnos varierar sjukdomsförloppet mellan individerna. Den kognitiva förmågan fluktuerar en del, men över lag försämras kognitionen över tid och leder till varierande grader av funktionsnedsättningar. Efter en demensdiagnos förväntas man leva mellan 3 och 15 år. Överlevnaden bland patienter med olika demensdiagnoser är inte särskilt väl studerat. Några studier har dock visat att typ av demenssjukdom, kön, ålder, och kognition påverkar prognosen. Patienter och anhöriga önskar ofta information om hur länge man förväntas leva efter en demensdiagnos. Detta är även viktigt för vård- och folkhälsoplanering.

Denna avhandling har två syften: det första är en grundlig beskrivning av patienter med subjektiva minnestörningar (SCI) och “mild cognitive impairment” (MCI), den typ av lindrig kognitiv störning som vanligen är en preklinisk fas i Alzheimers sjukdom för att på så sätt få ökad kunskap om den tidigaste detektbara fasen i Alzheimers sjukdom. Det andra syftet är att identifiera vilka faktorer som bidrar till variationer i dödsrisk för patienter med olika typer av demenssjukdomar.

Studie I är baserad på en patientdatabas från Minnesmottagningen vid Geriatriska Kliniken, Karolinska Universitetssjukhuset, Sverige. Uppgifterna samlades retrospektivt. I studie I ingår 993 patienter med diagnos av AD, lindrig kognitiv störning (MCI) eller

subjektiva minnestörningar (SCI). Artikeln innehåller beskrivande statistik och jämförelse mellan personer diagnosticerade med AD, MCI och SCI. En logistisk regressionsmodell (baserat på ålder, kön och biomarkörer i cerebrospinalvätska) skapades för att analysera vilka egenskaper hos MCI och SCI grupperna som ökade deras likhet med AD gruppen. Först skapades en modell som noggrant klassificerade AD, MCI och SCI individer. Resultaten från denna modell användes för att tilldela en sannolikhet för varje individ i grupperna att vara mer eller mindre "AD-lik" enligt modellen. Beskrivande resultat från studien visade att personer med SCI var yngre, hade högre utbildning, bättre kognition, mindre generaliserad kortikal och global atrofi, och mindre atrofi i medialtempralloberna än de med MCI och AD. Den statistiska regressionsmodellen med "AD-likhet" som beroende variabel visade att bland patienter med SCI var kardiovaskulära riskmarkörer, vitsubstans-skador, medialtemporallobs-atrofi och central atrofi kopplade till ökande "AD-likhet" innom modellen.

Studier II och III baseras på SveDem, Svenska Demensregistret, där incidenta demensdiagnoser i hela Sverige registreras. SveDem etablerades 2007 för att förbättra kvaliteten i vården av demenspatienter i hela landet. Med över 95 % av specialistenheterna anslutna till registret och fler än 45 000 registrerade individer erbjuder SveDem fantastiska möjligheter att utforska vilka faktorer som påverkar bland annat överlevnad efter en demensdiagnos.

Studie II och III använder data från SveDem för att utforska vilka faktorer som påverkar dödsrisken efter att en demensdiagnos ställts. I studie II analyserades 15 209 patienter som diagnostiserades vid specialistenheter och som följdes upp tills de avled eller slutet på uppföljningsperioden (i genomsnitt 2,5 år). Högre ålder, manligt kön, sämre kognition (definierad med Mini-Mental State Examination – MMSE), att bo i särskilt boende och användning av många läkemedel var kopplat till högre dödsrisk. Personer med AD hade lägre dödsrisk än de med andra demenssjukdomar och vaskulär demens hade den största risken i ojusterade analyser. I analyser kontrollerade för kön, ålder, antal läkemedel och MMSE blev frontallobsdemens den typ av demenssjukdom som hade störst dödsrisk. I studie III studerades sambandet mellan body-mass index (BMI) och dödlighet efter demensdiagnos bland 11 398 patienter. Högre BMI associerades med lägre

dödsrisk: risken var högst bland patienter med BMI under 18.5 kg/m^2, och lägst bland feta individer (BMI ≥30). Varje enhetsökning av BMI associerades med en minskning av dödlighetsrisken upp till BMI 29.9 för hela kohorten samt för män, och upp till ett BMI 24.9 kg/m^2 för kvinnor.

Sammanfattningsvis hade personer med AD, MCI och SCI olika egenskaper. SCI-patienter med högre risk för AD kunde identifieras med hjälp av några kliniska markörer som atrofi och kardiovaskulära riskfaktorer. Efter att demensdiagnosen har ställts är faktorer som ålder, att vara man, lägre MMSE, annan demensdiagnos än AD, annan sjuklighet, lägre BMI och att bo i särskilt boende kopplat till ökad dödlighet.

Key words: demens, subjektiva minnesstörningar, lindrig kognitiv störning, Alzheimers sjukdom, Lewy body demens, Parkinsons sjukdom med demens, blandad Alzheimer och vaskulär demens, vaskulär demens, epidemiologi, dödsrisk, kvalitetsregister, BMI.

ABBREVIATIONS

Aβ	Amyloid-beta
AD	Alzheimer's dementia
AD-C	Clinical Alzheimer's disease
AD-P	Pathological Alzheimer's disease
AIDS	Acquired immunodeficiency syndrome
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
BAI	Body adiposity index
BMI	Body mass index
BPSD	Behavioral and psychological symptoms associated with dementia
bvFTD	Behavioral variant frontotemporal dementia
CERAD	Consortium to Establish a Registry for Alzheimer's disease
CSDD	Cornell scale of depression in dementia
CSF	Cerebrospinal fluid
CT	Computed tomography
DAT	Dopamine active transporter
DLB	Dementia with Lewy bodies
DSM-5	Diagnostic statistic manual, 5th edition
DSM-IV	Diagnostic statistic manual, 4th edition
DXA	Dual-energy X-ray absorptiometry
FDG-PET	Fluoro-deoxyglucose positron emission tomography
FLAIR	Fluid attenuation inversion recovery
FTD	Frontotemporal dementia

FTLD	Frontotemporal lobe degeneration
GDS	Global deterioration scale
GDP	Gross domestic product
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICD-10	International classification of diseases, 10^{th} edition
IWG	International Working Group
LB	Lewy bodies
LBD	Lewy body dementias
LDL	Low density lipoprotein
LN	Lewy neurites
MCI	Mild cognitive impairment
MICS	Malnutrition inflammation complex syndrome
MMSE	Mini-mental State Examination
MND	Motor neuron disease
MRI	Magnetic resonance imaging
MTA	Medial temporal atrophy
NIA-AA	National Institute of Aging-Alzheimer's Association
NMDA	N-methyl-D-aspartate
OR	Odds ratio
PD	Parkinson's disease
PDD	Parkinson's disease with dementia
PET	Positron emission tomography
PiB-PET	Positron emission tomography (PET) with the Pittsburgh

	compound B
PY	Person-years
REM	Rapid eye movement
SCI	Subjective cognitive impairment
SD	Standard deviation
SEN	Sociedad Española de Neurología (Spanish Neurological Society)
SMR	Standardized mortality rate
SPECT	Single-photon emission computed tomography
TDP-43	Transactive response DNA-binding protein 43
TIA	Transient ischemic attack
US	United States
VaD	Vascular dementia
VLDL	Very low density lipoprotein
WHO	World Health Organization
WHR	Waist-height ratio
WML	White matter lesions

CONTENTS

1. INTRODUCTION

1.1 THE EVOLVING CONCEPT AND DEFINITIONS OF DEMENTIA

Dementia has accompanied humanity since the dawn of time and has been recognized as an illness associated with old age since the beginning of history.[1, 2] Aretaeus of Cappadocia may have been the first to draw the distinction between delirium, which he described as reversible, and dementia, which was permanent and progressive.[2] Both Hippocrates and Galen were aware that these disorders could arise either from a primary process to the brain or from secondary disease located in other organs of the body.[2] Cicero may have been the first to distinguish dementia from normal aging and to propose intellectual activity as preventive of mental decline.[3]

Alois Alzheimer's first description of a case of Alzheimer's disease (AD) did not immediately spark much subsequent research. This was possibly due to the fact that the author himself thought this disease to be rather uncommon. Indeed, according to Pubmed® there were only 47 publications containing the keyword "Alzheimer" between 1963 and 1973. The United States (US) congressional mandate which resulted in the creation of the National Institute of Aging in the US in 1974 changed this picture.[2, 4] Fourteen articles on "Alzheimer's disease" were published in 1974, 43 in 1975, and 110 in 1980. From there, the progression has been exponential, reaching 4 988 indexed publications during 2012. Other diseases, such as "dementia with Lewy bodies" and "frontotemporal degeneration" have joined the picture, and today dementia is widely understood as a collection of syndromes caused by an array of disorders of the brain.

The World Health Organization (WHO)[5] defines dementia as a syndrome due to disease of the brain, usually chronic or progressive, in which multiple cortical functions are disturbed with spared consciousness. A decline from previous cognitive functioning must be evident and delirium or major psychiatric disorder must be excluded as causes. The National Institute for Aging-Alzheimer's Association (NIA-AA) workgroup further stipulates that cognitive impairment must be determined through a combination of history-taking from a knowledgeable informant and cognitive testing. Furthermore, cognitive deficits must be present in at least two domains: memory, reasoning and

judgment, visuospatial, language, or personality and behavior.[6] This syndrome predominantly affects older individuals, but the disturbance goes beyond that expected for normal aging.

Several diagnostic criteria, such as those of the ICD-10 (International classification of diseases, 10th edition)[5] and the DSM-IV-TR and DSM-5 (Diagnostic statistic manual, 4th edition revised and 5th editions) exist for dementia (tables 1 and 2) ,[7, 8] and an array of guidelines and criteria exist for individual disorders.[5, 6, 9-13] However, there remain areas of overlap between disorders and between the preclinical or predementia phases of diseases and dementia.[9] These areas of uncertainty are the consequence of the limitations of all classification systems, as well as the wide range of presentations of biological disease.

Table 1.	ICD-10 diagnostic criteria for dementia*		
G1. Presence of all of the following	Impaired memory: both verbal and non-verbal.	Mild	Memory loss interferes in daily activities. Independent living can be maintained.
		Moderate	Independent living is impaired.
		Severe	Subject unable to retain new information, severe amnesia of old information, fails to recognize relatives.
	Impairment in other cognitive domains: judgment, planning, information processing, organizing… Subject previously had a higher level of functioning.	Mild	Impairment in activities of daily living, still independent. Requires help for complex tasks.
		Moderate	Subject is unable to function without assistance.
		Severe	Intelligible ideation is virtually absent.
G2. Awareness is preserved			
G3.Behaviour, emotional control and motivation are affected			
G4. G1 should be present for at least six months			

ICD-10: International classification of diseases, 10th edition.

*Adapted from World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. WHO, Geneva 1993.

Table 2. DSM-IV-TR diagnostic criteria for dementia*

1. Both of the following:
   A. Objectively demonstrated memory deficit
   B. At least one other cognitive deficit: aphasia, executive dysfunction, agnosia or apraxia
2. These deficits cause impairment of daily life activities
3. Social and occupational impairment must be present
4. There is a decline from a previous higher level of functioning
5. Delirium is excluded

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.
*Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000.

1.2 ALZHEIMER'S DISEASE

1.2.1 First description and current view of Alzheimer's disease

In 1906, Alois Alzheimer described the case of a 51 year old woman, "Auguste D", who presented dementia and in whom postmortem examination revealed amyloid plaques and neuritic tangles. In 1911 Alzheimer published a report in which he included a second case, that of a 56 year-old man who was proven to have exclusively plaque pathology. The histological sections have been preserved to this day which has allowed confirmation of Alzheimer's findings and exclusion of amyloid precursor protein (APP) mutations.[14, 15] Alzheimer himself was unsure about the nature of the condition, which he thought could represent an early presentation of senile dementia or a different entity entirely. These qualms were not shared by Emil Kraepelin, Alzheimer's supervisor and the world's most prominent psychiatrist at the time, who included the condition and called it Alzheimer's disease (AD) in his 1910 Textbook of Psychiatry.[3] Other pathologists gave validity to these histological descriptions,[3] but AD was still considered, for several decades, as a rare condition that only affected younger people. Regarding dementia presenting in older age, Kraepelin described how *""Past events gradually vanish from their memory, although often events of their childhood are recalled in their mind with surprising vividness (...)*" and that *"(...) particular the memory of recent events starts to reveal numerous and incomprehensible gaps (...)"*.[3] Together, Alzheimer and Kraepelin set the foundation stones for the concepts of young-onset and late-onset AD.

Today, AD is understood as a complex disorder in which the neuropathological disease (Alzheimer's disease pathology, AD-P) must be distinguished from its clinical manifestation (varying degrees of cognitive impairment and clinical syndromes caused by Alzheimer's disease, AD-C).[16, 17]

Two sets of research criteria are available for AD, both employing biomarkers.[18] The International Working Group (IWG) proposes criteria for "preclinical AD", further subdivided as "asymptomatic at risk for AD" and "presymptomatic AD", with the latter

group including presymptomatic subjects carrying autosomal dominant mutations for hereditary AD. Symptomatic individuals are classified as "AD" with subgroupings of "prodromal AD" (a mild cognitive impairment-MCI stage) and "AD dementia". The second set of criteria consists of the NIA-AA recommendations. When biomarkers are available, individuals are classified into an asymptomatic stage called "preclinical AD", an AD-MCI stage referred to "MCI due to AD" and a dementia stage "dementia due to AD". When biomarkers are not available, individuals are classified according to clinical criteria as "possible or probable AD" or "MCI". Table 3 compares both classifications.

Table 3. Comparison of IWG and NIAA-AA recommendations for the diagnosis of Alzheimer´s disease

	Pre-pathological	Presymptomatic		Symptomatic	
			AD-SCI stage	AD-MCI stage	AD-dementia stage
IWG		Preclinical AD Asymptomatic at risk for AD: abnormal biomarkers Presymptomatic AD: carriers of AD mutations		Prodromal AD	AD-dementia
NIA-AA*		Preclinical AD stages 1 and 2	Stage 3	MCI due to AD	Dementia due to AD
Time	Decades before diagnosis		10-20 years before diagnosis (?)	7-10 years before diagnosis (?)	Diagnosis

AD: Alzheimer´s disease. IWG: International Working Group. MCI: mild cognitive impairment. NIA-AA: National Institute for Aging-Alzheimer's Association. SCI: subjective cognitive impairment.

*For the NIA-AA the criteria given are those used in the presence of biomarkers.

1.2.2 Pathological Alzheimer's disease (AD-P)

AD neuropathologic change refers to the accumulation of senile β-amyloid (Aβ) plaques and neurofibrillary tangles (NFT) with varying degrees of intensity and distribution.[19] NFT are intraneuronal fibrils primarily composed of abnormal tau and can be visualized with histochemical stains or immunohistochemistry directed against tau or phospho-tau epitopes. In early stages, they may only be present in limbic areas but gradually involve other brain regions including cortex, subcortical nucleii and some brainstem regions.[20] The sequence of involvement starts in the entorhinal cortex, spreading to hippocampus and then neocortex, although there are exceptions.[20, 21] Senile plaques are extracellular deposits of Aβ peptides. When they are located at the center of a cluster of dystrophic neurites (which often have phospho-tau immunoreactivity) they are called neuritic plaques. Non-neuritic structures can present as diffuse plaques, cotton wool plaques, amyloid lakes and subpial bands.[20] Amyloid plaques are heterogeneous and it is currently believed that neuritic plaques have the greatest potential for neuronal injury.[20] Aβ deposition in the brain follows a distinct sequence begining with neocortex (Thal phase 1), followed by allocortical brain regions (Thal phase 2), diencephalic nuclei, striatum and cholinergic nuclei in basal forebrain (Thal phase 3), other brainstem nuclei (Thal phase 4) and cerebellar deposition (Thal phase 5).[22] It is possible for AD neuropathology to be present in individuals without cognitive impairment, predating symptom onset by years. For individuals with clinical symptoms, intermediate or high levels of AD pathology are considered sufficient to explain symptoms and confirm an AD diagnosis.[17, 19]

The cholinergic system is implicated in the genesis of AD: basal cholinergic neurons project to both cortex and hippocampal regions and degenerate in AD, possibly due to the disappearance of neurotrophic signals from these target sites. However, these connections might still be viable for some time after disease onset and "rescuing" them has become the focus of new therapeutical intervention studies.[23] Encapsulated cell biodelivery of nerve growth factor (NGF) targeted towards preserving these connections is a promising line of research.[24-26]

The Braak and Braak[27] criteria are still in effect for NFT, while the NIA-AA favors the Thal phases for amyloid plaques[20, 22] and the criteria from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) for neuritic plaque scoring.[28] Thus, the NIA-AA recommends an "ABC" score (Amyloid, Braak, CERAD) for AD neuropathologic changes (table 4). The NIA-AA also recommends thorough reporting on Lewy body (LB) and vascular pathology, as well as hippocampal sclerosis and transactive response DNA-binding protein 43 kDa (TDP-43) inclusions.[19, 20, 22]

Table 4.	NIAA-AA recommendations for classification of Alzheimer's disease neuropathological change*
A.	Thal Aβ plaque score
	A0: no Aβ or amyloid plaques
	A1: Thal phase 1 or 2.
	A2: Thal phase 3
	A3: Thal phase 4 or 5
B.	NFT stage
	B0: No NFTs
	B1: Braak stage I or II
	B2: Braak stage III or IV
	B3: Braak stage V or VI
C.	CERAD neuritic plaque score
	C0: no neuritic plaques
	C1: CERAD score sparse
	C2: CERAD score moderate
	C3: CERAD score frequent

Aβ: β-amyloid. CERAD: Consortium to Establish a Registry for Alzheimer's Disease. NFT: neurofibrillary tangles. NIAA: National Institute for Aging-Alzheimer's Association.

*Reproduced with permission from Bradley T. Hyman et al. National Institute on Aging – Alzheimer's Association guidelines on neuropathologic assessment of Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2012;8:1–13.

1.2.3 Clinical Alzheimer's disease (AD-C)

The typical clinical picture of early AD is characterized by insidious and progressive cognitive decline of sufficient gravity to meet criteria for dementia with two or more affected cognitive domains (tables 5 and 6). The amnestic presentation is the most typical, with deficits in episodic memory. Nonamnestic presentations include language presentations (word-finding deficits), visuospatial presentations, or executive dysfunction. Extensive vascular cerebral damage apparent in clinical history or imaging may not be present.[6] Insight may or may not be preserved and depressive symptoms are a common associated finding. Social graces and basic activities of daily living tend to be preserved until later in the course of the disease.[29]

Two nonamnestic presentations of AD deserve special attention. One is posterior cortical atrophy.[6] In this syndrome, elements of Balint's syndrome, comprising difficulty integrating the perception of the entire visual field, difficulty directing eye movements and grasping objects presented visually can combine with apraxia, Gerstmann syndrome and other more typical AD symptoms.[29] Another is logopenic-primary progressive aphasia. In this condition, the primary deficit is word-finding, although deficits in at least one other cognitive domain must be present to determine an AD diagnosis according to NIA-AA criteria.[6] Primary progressive aphasia can also be associated with frontotemporal dementia (FTD), especially in cases of agrammatic presentations. However, although subtyping primary progressive aphasia can help predict whether AD or FTD is involved, no clinical predictor is completely reliable.[30]

Table 5. ICD-10 criteria for Alzheimer´s dementia*

F00 Dementia in Alzheimer´s disease

A. The general criteria for dementia (G1 to G4) must be met (table 1)

B. No evidence for other causes of dementia (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus), systemic disorder (e.g. hypothyroidism, vitamin B12 or folic acid deficiency, hypercalcemia), or alcohol- or drug-abuse.

Comments: Neurofibrillary tangles and neuritic plaques in excess to normal aging must be found post-mortem in order to confirm the diagnosis.

ICD-10: International classification of diseases, 10th edition.

*Adapted from World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. WHO, Geneva, 1993.

Table 6. NIAA-AA clinical diagnostic criteria for dementia with Alzheimer´s disease*

Meets criteria for dementia and, in addition, has the following characteristics:

A. Insidious onset
B. Clear-cut history of worsening of cognition (...); and
C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
    i. Amnestic presentation
    ii. Non-amnestic presentations:
        - Language presentation: word-finding deficits are most prominent. Deficits in other cognitive domains should be present.
        - Visuospatial presentation. Spatial cognition, object agnosia, impaired face recognition, simultagnosia, and alexia. Deficits in other cognitive domains should be present.
        - Executive dysfunction. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease (...); or (b) core features of dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent /agrammatic variant primary progressive aphasia; or (e) evidence of another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

NIAA: National Institute for Aging-Alzheimer's Association.

*Adapted from McKhann et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer Dement 2011;7:263-269.

1.2.4 The preclinical and predementia stages of Alzheimer's disease

1.2.4.1 Subjective cognitive impairment: a preclinical syndrome

Subjective cognitive impairment (SCI) applies to a heterogeneous group of patients who present with cognitive complaints without hard evidence of neuropsychological decline.[31] Neurodegeneration is expected to begin several decades before clinical symptoms,[32, 33] and the MCI stage preceding dementia is calculated to last 7-10 years.[34] Thus, it is reasonable to search for the earliest stages of dementia among patients who present cognitive complaints without demonstrable impairment.[9, 35] SCI affects a large percentage of patients attending memory clinics worldwide[31, 36-38] and represents a relevant clinical problem. The concept has evolved since Reisberg defined the stage 2 of the Global Deterioration Scale (GDS),[39] which is equivalent to SCI, and now many support the existence of this syndrome as an early stage in neurodegenerative disease, particularly AD.[40, 41] This may be especially valid when biomarkers are available and suggestive.[9] In other cases, diagnosis is more controversial.

Nowadays AD is an established diagnosis but substantial grey areas still remain. MCI is even more heterogenous, with uncertainty remaining over the prognosis of many groups of patients. All these problems increase in SCI, by definition a diagnosis without demonstrable cognitive decline and with few "hard" variables, and in which research has historically focused on personality characteristics of patients and depression.[31] The heterogeneity between patients and study methods complicates the debate: while some studies focus on general population and ask about cognitive complaints,[42-51] others recruit patients from memory units.[52-54] Table 7 summarizes studies which include data on prevalence for SCI.

Table 7. Studies with data on the prevalence of subjective cognitive impairment*

Reference	Project	Year	Study design	Prevalence of cognitive complaints	Cognitive complaints w/o objective impairment	Age	N
Geerlings et al[50]	Amsterdam Study of the Elderly	1994	Population	10.81%	8.96%	65-84	3774
Jonker et al[36]	Review	2000	-	22.1-56%	-	-	-
O'Connor et al[47]	Hugh Hall Project	1990	Population	37%	-	≥75	273
Bassett and Folstein[42]	Eastern Baltimore Mental Health Survey	1993	Population	22%		18-92	810
Gagnon et al[44]	PAQUID study	1994	Population	33.50%		≥65	2726
Tobiansky et al[49]	Gospel Oak Study	1995	Population	25%		≥65	705
Jonker et al[45]	AMSTEL	1996	Population	22.10%		65-84	2537
Blazer et al[43]	EPESE	1997		56%		≥65	3079
Paradise et al[46]	45 and Up Study	2011	Population	12%		45-64	45532
Sachdev et al[55]	MAS	2010	Population	95.50%	58.1%	70-90	1037
Amariglio et al[56]	Nurse's Health Study	2011	Population; female nurses	72.70%	?	70-81	16964
Gallassi et al[57]		2010	Memory Unit	-	46.23%	-	92
Andersson[37]		2005	Memory Unit	-	38%		
Riedel-Heller et al[58]	LEILA 75+	1999	Population	39%		>75	322

AMSTEL: Amsterdam Study of the Elderly. EPESE: Established Populations for Epidemiological Studies

elderly. LEILA 75+: Leipzig Longitudinal Study of the Aged. MAS: Sydney Memory and Aging study. N: number of patients. PAQUID study: Personnes Agées QUID.

*Reproduced with permission from Sociedad Española de Neurología (SEN). Garcia-Ptacek S, et al. Quejas cognitivas subjetivas: hacia una identificación precoz de la enfermedad de Alzheimer [Subjective cognitive complaints: towards early identification of Alzheimer´s disease] Neurología. 2013. doi:10.1016/j.nrl.2013.02.007

Despite all these problems, the case is strong for including SCI as the earliest stage in an SCI-MCI-AD *continuum*. A growing body of evidence suggests that SCI patients are at increased risk of future cognitive decline,[51, 59-61] although some authors have found no association.[62] As can be seen in table 8, SCI is associated with future decline in longitudinal studies with odds ratios (OR) that range between 1.5 and 8.5 compared to controls. White matter lesions[59] and higher education strengthen the association between SCI and future decline.[60] It may be that individuals with higher education are sensitive to their own cognitive decline before neuropsychological testing can detect it, or that the ceiling effect of cognitive testing is particularly relevant in this group. Highly educated individuals might also have more cognitively demanding occupations, which could highlight even slight decline.

Subjects with SCI also differ from the general population in neuroimaging.[63, 64] Studies have demonstrated a reduction in hippocampal volume among SCI subjects compared to controls,[64] as well as volumetric reductions in medial temporal and frontotemporal areas[63] with the same distribution as in MCI patients, but less severe. Functional neuroimaging demonstrates increased activation in cognitive tasks in AD, MCI and apolipoprotein E (APOE) ε4 carriers,[65, 66] indicating the presence of compensatory recruitment. The intensity of this hyperactivation has been correlated with increased subsequent decline.[65] This pattern has been reproduced in SCI, with subjects presenting an increased cortical activation in prefrontal dorsolateral and left premotor areas during a memory coding task in one study,[67] and an increase in thalamic, posterior cingulus, bilateral caudate and left hippoccampus and parahippoccampic region in another.[68] Additionally, fluoro-deoxyglucose positron emission tomography (FDG-PET) has shown decreased metabolism in SCI subjects in parahippoccampus, parieto-temporal, inferior frontal, fusiform gyrus and thalamus, replicating findings in healthy subjects with high risk for AD (autosomic dominant familial AD, high family prevalence of AD or APOE ε4 homocygotes), and in MCI subjects.[33]

SCI has also been linked to AD pathology. Two studies found a relationship between cognitive complaints before time of death with AD pathology in autopsy.[69,70]

Another found a higher frequency of AD-pattern biomarkers in cerebrospinal fluid (CSF) of SCI subjects compared to controls.[71] The current theory on the evolution of biomarkers in AD proposes an early drop in CSF Aβ while the increase in tau occurs at later stages.[54] If SCI is part of the AD continuum, biomarkers should correspond to the earlier stages of this timeline. Indeed, CSF Aβ42 has been shown to correlate with performance in semantic and working memory tasks in SCI and controls, while tau predicts cognitive performance better in MCI individuals.[72]

Amyloid load demonstrated by PET with the Pittsburgh compound B (PiB-PET) shows correlation with atrophy in SCI subjects, but not in controls.[73] Chatélat et al[74] found that healthy subjects with high PiB deposit had larger temporal lobes than their low PiB comparisons, suggesting that only subjects with constitutionally large temporal lobes are able to remain asymptomatic with a high amyloid load, or that amyloid itself causes the temporal lobes to enlarge in an early stage. The inverted U relationship that has been found between amyloid load and cortical volume strengthens this last hypothesis.[53] In Chatélat's study, SCI subjects with high amyloid had lower temporal volumes than healthy subjects with high amyloid, possibly indicating the beginning of a reduction in temporal volume.[74] However, these studies were cross-sectional. Without longitudinal studies it is impossible to know whether these findings reflect different patient populations or the natural course of the disease.

Table 8. Studies on cognitive outcome of subjective cognitive impairment*

Reference	Study	Year	N	Cognitive assessment	Follow-up	SCI predicts decline	Strength of association
Dufouil et al[59]	EVA	2005	555	CDS, DSST, FTT, AVLT, CES-D	2 years	+	OR 1.5 without WML, 8.5 with WML
Geerlings et al[50]	AMSTEL	1999	2169	MMSE, CAMCOG	3.2 years	+	OR 2.11
Van Oijen et al[60]	Rotterdam Study	2007	6927	MMSE, GMS, CAMDEX	9 years	+	OR 1.53-2.33 depending on educational level
Jorm et al[51]	Camberra	2001	331		7-8 years	+	
Wang et al[62]	KINDS	2000	543	CASI, GDS-S	3 years	-	

AMSTEL: Amsterdam Study of the Elderly. AVLT: Rey Auditory Verbal Learning Test. CAMCOG: Cambridge Cognition Examination. CAMDEX: Cambridge Mental Disorders of the Elderly Examination. CASI: Cognitive Abilities Screening Instrument. CDS: Caroll Depression Scales. CES-D: Center for Epidemiological Studies Depression scale. DSST: Digit Symbol Substitution Test. EVA: Epidemiology of Vascular Aging study. FTT: Finger Tapping Test. GDS-S: Geriatric Depression Scale-Short version. GMS: Geriatric Mental Status interview. KINDS: Kinmen Island Neurologic Disorder Survey study. MMSE: Mini-mental State Exam. N: number of patients. OR: odds ratio. SCI: subjective cognitive impairment. WML: white matter lesions.

* Reproduced with permission from Sociedad Española de Neurología (SEN). Garcia-Ptacek S, et al. Quejas cognitivas subjetivas: hacia una identificación precoz de la enfermedad de Alzheimer [Subjective cognitive complaints: towards early identification of Alzheimer´s disease] Neurología. 2013. doi:10.1016/j.nrl.2013.02.007

1.2.4.2 Mild cognitive impairment due to Alzheimer's disease: the symptomatic predementia stage

MCI describes a state of noticeable cognitive impairment in which independence in functional abilities is preserved.[75] When the cause is AD, MCI can be considered a predementia stage in the AD disease course. The NIA-AA requires for diagnosis the existence of a concern regarding drop in cognition from the patient's previous level, demonstrable impairment in one or more cognitive areas with preservation of independence despite mild problems in complex functional tasks. If social or occupational impairment becomes significant, the patient is diagnosed with dementia and the diagnosis of MCI is no longer applicable.

1.2.5 Diagnostic tools: the role of biomarkers

Biomarkers can be defined as anatomic, physiological or biochemical *in vivo* parameters that reflect specific features of disease-related pathophysiology. For its 2011 criteria, the NIA-AA focused on those which were sufficiently established as being linked to AD and divided them into two categories based on their specificity.[17] Thus, one category includes biomarkers of Aβ accumulation, as demonstrated by amyloid PET or low CSF Aβ42. Another category includes biomarkers of neuronal degeneration or injury, such as high CSF tau, decreased FDG uptake in PET in temporoparietal cortex, and atrophy in structural magnetic resonance imaging (MRI) in areas prone to AD pathology, such as medial and lateral temporal lobes, parietal and prefrontal cortex.[9, 76] Biomarkers suggestive of amyloid pathology appear first in the disease process, anytime between 10 to 20 years before clinical symptoms. Biomarkers of neuronal injury and dysfunction come later, maybe shortly before clinical onset, and parallel cognitive worsening.[17]

Following the NIA-AA criteria, biomarkers are used in the preclinical phase to establish the presence of AD-P in asymptomatic or subtly symptomatic research subjects. In the MCI and AD phases, biomarkers are complementary to clinical diagnosis, which can be made exclusively employing the clinical criteria in settings where biomarkers are

unavailable.[17, 75] In MCI, according to the NIA-AA, biomarkers remain a tool for research, not for routine clinical assessment.[75]

1.3 VASCULAR DEMENTIA

Vascular dementia (VaD) has been defined as the loss of cognitive function with interference with activities of daily living resulting from ischemic or hemorrhagic cerebrovascular disease or from cardiovascular or circulatory disturbances that affect brain function.[77] Vascular causes were considered the main origin of cognitive decline until the 70s and 80s, when the focus shifted towards neurodegenerative causes of dementia.[78] The pendulum may now be swinging back, with a renewed interest in vascular pathology and its interaction with AD.[79]

VaD is often cited as the second most common type of dementia after AD,[77, 80] although estimates of prevalence vary depending on the definition employed.[78] Unlike AD, VaD is more prevalent in men[77] and memory disturbance is not a principal feature.[78] The clinical picture can be varied, ranging from post-stroke dementia to lacunar state or Biswanger's disease.[77] Clinical manifestations depend on the affected brain regions and can span from aphasia or apraxia for cortical lesions to executive dysfunction and gait abnormalities for subcortical pathology.[79] Clinical course is variable, with acute or subacute onset, which can improve, stabilize or decline in a gradual or step-wise fashion.[79] Unlike the definition of AD, which describes a specific clinical picture coupled with its anatomopathological correlate, VaD groups a range of clinical presentations with a broader cardiovascular cause.

1.4 MIXED ALZHEIMER´S AND VASCULAR DEMENTIA

The boundaries between VaD and AD are indistinct. Cardiovascular risk factors, including insulin resistance and hypertension, are linked both to AD and VaD.[78] APOE ε4 allele is a risk factor for AD but also increases the likelihood of cerebral infarcts.[81] Most elderly patients with dementia have AD pathology coexisting with cerebrovascular

lesions[77, 81] which could amplify the effects of AD plaques and tangles.[77] In the Rush Religious Orders Study, vascular pathology was prevalent: clinically unrecognized macroscopic infarcts were frequent and commonly occurred in the context of AD pathology.[81] Infarcts independently added to the likelihood of dementia and almost half of clinical AD patients also had vascular pathology.[81] Twenty percent of autopsy cases with AD pathology in CERAD did not have clinical dementia: cerebrovascular lesions may be the tipping point that leads to clinical symptoms in persons with AD pathology.[77] It is unclear whether both disease processes have an additive effect in the progression towards dementia or whether they function synergistically, enhancing and accelerating cognitive decline.[78] In the Religious Orders study, macroscopic infarcts increased the risk of dementia in an independent, non-synergistic manner.[81] This overlap can indicate that risk factors for AD might act through cardiovascular, and not amyloid pathological pathways[81] and expands the spectrum of possible therapeutic strategies.

Furthermore, a proportion of patients present with both AD and VaD clinical features. The term mixed dementia is often used to define this group, with patients demonstrating varying degrees of memory and executive or other dysfunction accompanied by evidence of cerebrovascular disease.

1.5 LEWY BODY DEMENTIAS: DEMENTIA WITH LEWY BODIES AND PARKINSON'S DISEASE WITH DEMENTIA

Initially described as separate entities, it is now recognized that dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) share a common pathophysiology and can be understood as two expressions within a pathological *continuum*.[82] The umbrella term Lewy body dementias (LBD) is now being proposed.[82] In this disease, neuronal inclusions of alfa-synuclein forming Lewy bodies (LB) and Lewy neurites (LN) are accompanied by neuronal loss, often with varying degrees of AD pathology. The prevalence of dementia among PD patients is around 25% with a dementia risk that increases with disease duration. Less information is available for the

prevalence of DLB, which is probably underestimated.[83] One review reported percentage of total dementia population ranging from 0-24%.[84]

1.5.1 Dementia with Lewy bodies

LB and LN are pathologic aggregations of alpha-synuclein affecting brainstem, limbic and cortical regions.[85] In DLB, these neuropathological findings accompany a clinical LB syndrome characterized by often rapidly progressive mental impairment with disproportionate attention, problem solving and visuospatial difficulties, accompanied by fluctuations in cognitive function, visual hallucinations, parkinsonism and increased sensitivity to neuroleptic treatments.[86] Rapid eye movement (REM) sleep behavior disorder, autonomic dysfunction, systematized delusions and hallucinations in other modalities can also be present. Although the first consensus criteria for the diagnosis of DLB accepted any intensity of LB in neuropathology as criteria for diagnosis,[86] it is now recognized that up to 60% of pathologically confirmed AD cases may also have some LB pathology.[85] For this reason, the new diagnostic criteria consider the intensity and extension of LB pathology, as well as the presence and severity of accompanying AD pathology to determine if a case is likely to be associated with a DLB clinical syndrome[13] Low striatal uptake in functional imaging of dopamine active transporter (DAT) is common to PD and DLB, and can help distinguish them from AD. Occipital hypoperfusion or hypometabolism without accompanying atrophy is another suggestive feature (table 9).[13]

1.5.2 Parkinson's disease with dementia

Dementia is a common outcome in PD, occurring 10 or more years after onset of motor symptoms. PD is pathologically characterized by LB and LN in the substantia nigra together with loss of dopamine in the nigrostriatal tract.[87] The cognitive syndrome is remarkably similar to that of DLB, with the same cognitive profile and other identical features such as autonomic dysfunction, sleep disorders, neuroleptic sensitivity and neuropsychiatric symptoms.[85] However, age at onset, temporal course relative to

parkinsonian motor symptoms and levodopa response are different. Thus, the distinction of both entities relies only on the temporal sequence of parkinsonian and cognitive symptoms. An arbitrary cut point of 1 year or more separation between appearance of parkinsonian and cognitive symptoms has been used to distinguish PDD from DLB[10] (table 9). Thus, PDD describes the appearance of the common clinical cognitive syndrome within well-established PD, while in DLB parkinsonian and cognitive features would appear simultaneously.[85] Critics of this classification argue that the distinction is arbitrary, that both diseases share the LB as a pathological basis, suggesting that they are manifestations of the same disease.[82, 85] Furthermore, studies on incident or early PD have demonstrated that a significant proportion of these patients already display some cognitive impairment at the time of diagnosis,[87, 88] with 8% scoring under 24 on the Mini Mental State Examination (MMSE) in one cohort study, with a profile that suggested frontostriatal, temporal lobe or global involvement.[87]

Table 9. Comparison between dementia with Lewy bodies and Parkinson's disease with dementia current diagnostic criteria*

Current DLB Consortium Criteria[13]

Central feature (required for possible or probable DLB)

a. Progressive dementia severe enough to interfere with normal social or occupational function
b. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent

Core features (2 are required for probable, 1 for possible DLB)

a. Fluctuating cognition
b. Recurrent visual hallucinations
c. Spontaneous parkinsonism

Suggestive features (if 1 or more is present with at least 1 core feature, probable DLB; in the absence of core features, possible DLB)

a. REM sleep behaviour disorder
b. Severe neuroleptic sensitivity
c. Low dopamine transporter uptake in the basal ganglia

Supportive features (commonly present but not proven to have diagnostic specificity)

a. Repeated falls and syncope
b. Transient unexplained loss of consciousness
c. Severe autonomic dysfunction
d. Non-visual hallucinations
e. Systematized delusions
f. Depression
g. Relative preservation of medial temporal lobe structures
h. Generalized low uptake on SPECT/PET with reduced occipital activity
i. Abnormal MIBG myocardial scintigraphy
j. Prominent slow wave activity on EEG with temporal lobe transient sharp waves

A diagnosis of DLB is less likely if

a. Cerebrovascular disease or other physical illness are sufficient to account for part or all of clinical picture
b. Parkinsonism does not appear until severe dementia

Current Criteria for PDD[10]

Core features (both required for possible or probable PDD)

a. Diagnosis of PD according to Queen Square Brain Bank Criteria
b. Dementia developing in the context of established PD, with cognitive impairment in more than 1 domain and severe enough to impair daily life

Associated clinical features (typical profile of cognitive deficits must be present for probable, but not possible, diagnosis)

a. Typical cognitive profile: Impairment in at least 2 of the following domains: a) attention (which may fluctuate) b) executive function, c) visuospatial function d) free recall (which usually improves with cueing)
b. Presence of behavioural features supports but absence does not exclude diagnosis, and include apathy, depressed or anxious mood, hallucinations, delusions, and excessive daytime sleepiness

A diagnosis of PDD cannot be made if

a. Cognitive and behavioural symptoms appear solely in the context of other conditions such as systemic diseases, drug intoxication, or major depression
b. Patient meets criteria for probable vascular dementia

The temporal sequence of symptoms guides differential diagnosis of DLB and PDD

a. In DLB the dementia develops before or within one year of spontaneous parkinsonism
b. In PDD the dementia develops within the context of established PD

DLB: Dementia with Lewy bodies. EEG: Electroencephalogram. MIGB: metaiodobenzylguanidine. PD: Parkinson´s disease. PDD: Parkinson´s disease with dementia. PET: Positron emission tomography. REM: rapid eye movement. SPECT: Single-photon emission computed tomography.
*Courtesy of Dag Aarsland; Center for Age-Related Diseases, Stavanger University Hospital, Norway.

1.6 FRONTOTEMPORAL LOBAR DEGENERATION

A common cause of presenile dementia, frontotemporal lobar degeneration (FTLD) can present with a spectrum of clinical syndromes, from language or motor to behavioral dysfunction.[89, 90] The pathology underlying this condition is unpredictable and heterogeneous, although neuronal loss, gliosis and spongiosis of frontotemporal distribution are its hallmark.[91, 92] Neuropathological abnormalities can be represented by tau-positive inclusions and insoluble tau with predominance for 3 microtubule-binding repeats (3R), tau-positive inclusions and insoluble tau with 4 microtubule-binding repeats (4R), a combination of both, or ubiquitin-positive/tau negative inclusions.[92] Around 40% of patients have a family history of disease, but only in some cases has the genetic cause been identified, usually in the genes of microtubule associated protein tau or progranulin, and there is considerable overlap with corticobasal degeneration.[91]

The most frequent syndrome in FTLD is behavioral variant frontotemporal dementia (bvFTD), characterized by a progressive deterioration of personality, social behavior and cognition due to degeneration of frontal and anterior temporal lobes.[89, 90] The International Consensus Criteria for bvFTD were published in 2011 and require progressive deterioration of behavior or cognition reported by a reliable informant and a combination of clinical and neuroimaging changes[89] (table 10). Possible bvFTD may be diagnosed by the presence of three symptoms among a list of signs of behavioral disinhibition, apathy, loss of empathy, perseverative or compulsive behavior, hyperorality or dietary changes, or a dysexecutive neuropsychological profile. If neuroimaging shows frontal and/or anterior temporal atrophy in MRI or computed tomography (CT), or hypoperfusion or hypometabolism is demonstrated through PET or single photon emission computed tomography (SPECT), the patient receives a diagnosis of probable bvFTD. A definite diagnosis requires compatible FTDL pathology or the presence of a known pathogenic mutation.[89] These criteria display high sensitivity (86%) for bvFDT,[89] but issues arise when seeking objective standards for behavioral symptoms, since the line between a jovial personality and pathological disinhibition is a thin one and might depend, among other factors, on culture, age and social context. Furthermore, the

insidious nature of these symptoms often leads to a psychiatric misdiagnosis and the lack of insight typical of bvFTD patients complicates the picture.[90] Early diagnosis in this condition is critical: progression is fast, behavioral abnormalities can be disturbing and difficult to control and survival, averaging 5.4 years after diagnosis, is among the lowest of the dementias.[93] Exceptions are phenocopy cases: of unknown ethiology, these cases present behavioral features compatible with bvFTD without imaging abnormalities or functional decline.[93] Conversely, motor neuron disease (MND) can be part of the clinical picture and survival of those patients is dramatically reduced.[94]

Another form of presentation of FTLD is primary progressive aphasia in which speech is predominantly affected. Primary progressive aphasia can have other causes, among them AD, but both the non-fluent and semantic variants present FTLD pathology in around 70% of cases.[90]

Table 10. International consensus criteria for behavioural variant frontotemporal dementia*

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD:

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (…).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

A. Early behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:

A.1 Socially inappropriate behaviour

A.2 Loss of manners or decorum

A.3 Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:

B.1 Apathy

B.2 Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:

C.1 Diminished response to other people's needs and feelings

C.2 Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:

D.1 Simple repetitive movements

D.2 Complex, compulsive or ritualistic behaviours

D.3 Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:

E.1 Altered food preferences

E.2 Binge eating, increased consumption of alcohol or cigarettes

E.3 Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:

F.1 Deficits in executive tasks

F.2 Relative sparing of episodic memory

F.3 Relative sparing of visuospatial skills

III. Probable bvFTD

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (…)

C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:

C.1 Frontal and/or anterior temporal atrophy on MRI or CT

C.2 Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

bvFTD: behavioral variant FTD. CT: Computer tomography. MRI: Magnetic resonance imaging. PET: positron emission tomography. SPECT: Single-photon emission computed tomography.
*Reproduced with permission from Oxford University Press. Rascovsky K et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134(pt9): 245

1.7 BODY MASS INDEX

A number of measures of body weight and adiposity have been proposed as markers of nutritional status and cardiovascular risk.[95, 96] The standardized height-weight tables published by the Medico-Actuarial Mortality Investigations (a life-insurance company) in 1912 are an early example of this effort, with weight-height units following soon after.[96]

Galileo Galilei is credited[97] with being the first to describe the square-cube law, which states that when a shape is scaled up in size, its volumetric increase is proportionally greater than the increase of its surface. In fact, volume increases proportionally to the cube of the multiplier, while area is proportional to the square of the multiplier.[98] This has important implications in all areas of science, and explains why larger animals have thicker bones than would be expected from the scaled-up structures of their smaller counterparts.[99] Hence, if the body shape is assumed to remain constant regardless of height, then weight (W) would be proportional to the third power of height (H) as is represented by Rohrer's index (W/H^3).[96] Fulton's condition factor, based on weight divided by the third power of length ($100 \times W/L^3$) was introduced at the end of the 19th century[100] as a measure of "fatness" or "well-being" in fish.[97] Livi's *indice ponderale* (ponderal index) captured the idea by employing the cube root of body weight divided by height, and was widely employed in pediatric populations.[96] Cubic height-weight ratios are particularly suitable for organisms that display isometric scaling, in which proportions remain the same with changes in size. This is applicable to fish and some reptiles. However, mammals typically display allometric scaling, with changing proportions throughout development, and differing proportions between individuals of different sizes.[101]

Quételet recognized these difficulties in 1842.[102] He observed that, except for the first year after birth, where the square-cube law is still somewhat observed, weight increase was slower than predicted in children. Thus, a scaling power of 3 would represent the growth of babies; a power of 2 for children and 2.5 would be adequate for

adults. However, his final formula employed W/H^2 and has become the most widespread weight-height ratio in use:

$$Body\ mass\ index\ (BMI) = \frac{weight\ (kg)}{[height\ (m)]^2}$$

In 1972, Keys et al[96] contended that this quadratic measure correlated best with skinfold and body density measurements and proposed the term *body mass index* (BMI). According to these authors, BMI had the advantage of being the least correlated with height, with less than 1% of the variance in their analyses accounted for by regression of BMI and height.[96] Since then, BMI has become the go-to height-weight ratio, used for assessment of nutritional status[103] and health-promoting recommendations.[95] It is easy to obtain and easily reproducible,[95] and its relationship to morbidity, particularly cardiovascular, has been acknowledged in medical literature since the 70s.[104, 105] The World Health Organization uses BMI to classify underweight, normal weight and obesity in adults. The cut-points for these categories may be seen in table 11.

Table 11. World Health Organization classification of BMI (kg/m^2)

Underweight	Under 18.5
Normal range (with additional cut-points)	18.5-22.9
	23-24.9
Overweight	25-29.9
Obese	
Obese class I	30-32.5
Obese class II	35-39.9
Obese class III	40 and above

BMI: body mass index.

WHO classification of BMI with additional cut points. Adapted with permission from WHO, BMI classification. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed October 29th, 2014.

BMI is a tool for gauging body shape, but says nothing about body composition. It is particularly inaccurate in athletes, who have a high lean mass, and is gender, age and race specific. [106, 107] Adiposity, particularly visceral fat, is thought to be the main driver of the excess cardiovascular risk found in obese individuals.[108] Since BMI doesn't distinguish between fat tissue and lean muscle mass, it could be a poor marker of the kind of weight excess that causes cardiovascular risk. Furthermore, fat distribution is critical. In 1947 Jean Vague first proposed that excess upper body fat (typical of men) carried a higher risk of cardiovascular complications than fat carried in the gluteal-femoral areas (typical of women).[109] This finding has since been abundantly confirmed. Despite having higher overall percentage of body fat,[110] only 10% of women's fat is visceral, whereas this reaches 20-25% for men.[108] Steroid hormones modulate the accumulation of visceral fat, which increases after menopause in women until their cardiovascular risk rises to match that of men. Age, stress, ethnicity, physical exercise, diet and genetic factors influence the accumulation of visceral fat,[108] which has been linked to incident coronary heart disease, myocardial infarction and type 2 diabetes,[102,104,108, 110] and malignancies such as prostate, breast and colorectal cancers.[110] Visceral fat is thought to be a cornerstone in the metabolic syndrome. Characterized by an array of cardiovascular risk factors comprising abdominal obesity, hypertension, dyslipidemia, pro-inflammation, prothrombosis and insulin resistance, metabolic syndrome is associated with a significantly increased risk of cardiovascular disease.[111] Current evidence suggests that visceral fat, more than any other marker, correlates with the presence of metabolic syndrome and C-reactive protein.[108] Visceral fat tissue is hormonally active and inversely correlates with circulating adiponecting, a protective antiangiogenic factor.[110] Lipolysis also triggers the release of free fatty acids, which reach the liver and participate in non-alcoholic fatty liver disease. These fatty livers release very-low-density lipoproteins (VLDL), which carry fat to be accumulated in other organs.

The most precise techniques for measuring body fat are often also the most invasive and least practical. In 1972 Keys described measuring body density by *"weighing the subject completely under water, correcting for the air in the lungs and respiratory passages(...)"* with a mouthpiece valve that provided 100% oxygen for inspiration and collected expired gas, which was subsequently measured and analyzed.[96]

These cantankerous methods have been surpassed by CT and MRI volume measurements, the current gold standards for measuring body fat.[110] However, these methods are still expensive and time-intensive, and have little place outside of research study protocols. Dual-energy X-ray absorptiometry (DXA) might be an alternative, with a margin of error, when compared to MRI, under 3% for all fat modalities.[112] Echographic and impedance measures of body fat are somewhat simpler, but also less accurate. For reasons of accessibility and convenience, biometric measures remain the most extensively used in clinical practice. Table 12 shows the advantages and disadvantages of different methods of measuring body fat.

Table 12. Advantages and disadvantages of different methods of measuring adiposity

	Method	Accessibility	Cost	Correlation to body fat	Correlation to cardiovascular risk	Correlation to mortality	Caveats
Biometric indexes	Weight	high	low	low[107]	low[107]		
	Height	high	low	moderate inverse[107]	very low[107]	low[113]	
	Waist	high	low	low[107]	good[107, 114]	good[114]	
	Hip	high	low	moderate[107]	low[107]		
	BMI	high	low	good[107]	fair[107, 114]	good[114]	age, gender, race dependent
	BAI	high	low	high[106, 107]	low[107]		
	WHR	high	low	good[115]	high[114]	good[114]	
	Skin-fold caliper measure	moderate	low	good[116]			
	WHtR	high	low	good[115]	good[114]	good[114]	
Imaging	MRI	low	high	gold standard	high[117]		examination time
	CT	low	moderate	gold standard	high[118]		radiation
	DXA	intermediate	moderate	gold standard (-)[112]			
Other	Pletismography	very low	high	gold standard			

BAI: body adiposity index. BMI: body mass index. CT: computer tomography. DXA: dual X-ray absorptiometry. WHR: waist hip ratio. WHtR: waist height ratio.

Several measures and indexes have been proposed to capture body composition and fat distribution.[108] Measuring waist circumference is perhaps the simplest; measures over 90 cm in men[114, 119] and 80 cm in women[114, 119, 120] are associated with excess risk, but this depends on the ethnicity of the population studied. Nonetheless, waist circumference does not distinguish between visceral and subcutaneous fat. Although abdominal fat is part of the metabolic syndrome, studies now suggest that, contrary to visceral fat, subcutaneous fat might be beneficial, absorbing energy surplus and somewhat compensating for the excess risk from visceral fat.[108] Assuming that subcutaneous fat accumulation is generalized, one possible solution would be to obtain a hip circumference measurement and calculate a waist-hip ratio (WHR), thus accounting for subcutaneous fat.[110, 121] This assumes that subcutaneous fat is distributed homogeneously between the two regions and that it has the same metabolic properties. A correlation has been described between the WHR and the ratio of visceral to subcutaneous fat as measured cross-sectionally in CT.[110] The type of subcutaneous fat that accumulates in the glutefemoral area may be especially beneficial and has been associated with a favorable adiponektin profile.[121] In practical terms, waist circumference, alone or relative to hip circumference, [121] has been proven to be related with cardiovascular risk and mortality.

Another interesting measure is the body adiposity index (BAI), which is based on the division of hip circumference by the 1.5 power of height.[106] This index was originally developed in a Mexican American population in the context of a gestational diabetes mellitus study. Adiposity measured by DXA was correlated with a number of biometric indexes, and BAI emerged as the most informative. The final formula for BAI is shown below:

$$Body\ adiposity\ index\ (BAI) = \frac{height\ circumference\ (cm)}{[\ height\ (m)\ ]^{1.5}} - 18$$

The BAI index was then validated on a second African American population. Since the proportion of body weight which corresponds to fat is higher in women, men

and women with the same BMI have very different proportions of fat. This is not a problem with BAI, where the relationship between BAI and percentage adiposity is not different between genders.[106] Furthermore, by validating the index in different ethnic populations, BAI might avoid some of the problems encountered by BMI in describing adiposity across ethnicities. However, the critical question with biometric indexes is how they correlate to health. In one study that included several ethnic populations, BAI was the index with the worst correlation to lipid profile, blood pressure and glucose, while BMI, waist circumference, waist-hip ratio, and simple waist-to-height ratio correlated better.[122] BAI may show a stronger correlation with fat percentage than BMI, but BMI might be more precise in older men and in persons with extremely low or high body fat percentages.[123] BMI and waist circumference show a stronger association to cardiovascular risk markers than BAI.[124] Yet another study compared BMI, BAI, waist, hip, height, weight, percentage body fat as measured by DXA and cardiovascular traits including systolic and diastolic blood pressure, carotid intima-media thickness, fasting lipid parameters and metabolic clearance of insulin.[107] When BMI and BAI were compared, BMI better represented lipid profile, fasting glucose, carotid intima thickness, adiponectin, metabolic clearance of insulin and diastolic blood pressure. BAI was only superior to BMI in predicting percentage of body fat in pooled data: when data was sex stratified, BMI proved better.[107]

This shows that, despite its limitations, BMI has proven to have a robust correlation with cardiovascular risk and all-cause mortality.[107, 122, 124, 125] BMI, abdominal circumference and subcutaneous fat area are all closely correlated.[126] BMI is moderately or strongly correlated with a number of cardiovascular traits and body fat percentage.[107] It is difficult to determine which biometric index is best, but BMI has proved better than BAI in a number of measures, and could be superior to other indexes as well. In one study on sickness leave from work, all measures of obesity predicted paid absence from work, with BMI showing the strongest correlation.[127]

Furthermore, the case can be made that BMIs popularity justifies continued use. Height and weight are particularly accessible measures and possibly the only ones that

can be accurately self-reported. Despite caveats on underestimation of weight and overestimation of height in self-reported measures, almost everyone is aware of their own height and weight – the same cannot be said for waist or hip circumferences. Moreover, many patients know their own BMI measures and understand what they represent, which makes it a useful tool for patient information and science popularization.

1.8 EPIDEMIOLOGY OF DEMENTIA

Estimates on the prevalence of dementia vary between 5 and 7% of the population over 60,[128] with 45% of population over 85 affected by dementia.[129] The ongoing worldwide demographic transformation translates as an increasingly aging population, particularly in developing nations.[128] China, India and Latin America, in particular, could soon find themselves with a higher percentage of older people without sufficient working-age adults to support them. Prevalence of dementia increases exponentially with age, doubling for every 5.5-7 year increment in age.[128] Thus, the worldwide prevalence of dementia was 24.3 million in 2005,[130] 35.6 million in 2010,[128] and is expected to almost double by 2025.[128] This increase in number of people with dementia will be unevenly distributed, varying with underlying regional demographics. Countries with a stable aged population, where dementia prevalence is already highest, can expect the lowest increase, which will still represent a 40% increase in Europe and 60% in North America. Regions which start with low prevalence and are experiencing demographic transformations and population growth, such as North Africa and the Middle East, can expect 120 to 150% increase in incident cases. In Latin America, different regions will experience different evolutions, conforming to the first or second groups. Other regions already start with a high prevalence, but growing populations determine a drastic increase in number of cases, even if incidence is less affected. This scenario is valid for China, India, the South East and Western Pacific with increases of 100-120% of cases. A special case is Sub-Saharan Africa, where the crippling high mortality from human immunodeficiency virus (HIV) infection and infant deaths impede the demographic transition.[128] Thus, the biggest increase in the burden of dementia is expected to occur in low and middle income countries with the exception of Sub-Saharan Africa.[128]

These estimates assume no changes in dementia risk, so studying changes in trends in dementia incidence becomes paramount.[131] Although the increase in global prevalence is evident, it is possible that some specific groups and locations may experience decreases in incidence. If so, studying these groups could be crucial to identifying effective preventive strategies. Studies on secular trends in dementia incidence are methodologically difficult because of the long intervening periods, with changes in diagnostic criteria[131] and patient help-seeking behaviors. It is likely that diagnosis is progressively occurring earlier in the disease process and being extended to patients with other co-morbid conditions. Some studies have shown stable dementia prevalence,[132, 133] while others propose a decline in incidence.[131] Changes in prevalence estimates must be compared to trends in survival after diagnosis: if survival after diagnosis is increasing over time, unchanged prevalence estimates translate a decrease in the incidence of dementia. A recent study compared two cross-sectional surveys of the greater Stockholm area carried out 20 years apart with the same diagnostic criteria.[131] Compared to the population studied in the 80s, the more recent population proved to be older, with more years of formal education and a lower percentage of women. The persons with dementia from the recent cohort also had higher MMSE scores. Age- and sex-standardized prevalence for dementia was not different between the two cohorts. After controlling for year of birth, the more recent cohort presented with a lower OR of dementia diagnosis, and this reduced risk was particularly apparent among men. Both cohorts included follow-up: the 2001 cohort had lower mortality for all participants and for those diagnosed with dementia. This implies that the incidence of dementia in this region is decreasing.[131]

Another two-wave study was conducted in Zaragoza, Spain, and showed stable dementia prevalence between different cohorts examined in the 90's and 00's.[134] The age-adjusted prevalence of dementia among men had decreased in the more recent cohort, while the general population mortality in the area had gone down over time. If this were also true for patients with dementia, it would hint at decreased dementia incidence between the two cohorts.[134] The first cohort was examined in 1994, with follow-ups in 1997 and 1999, allowing for direct incidence calculations: according to this study, overall dementia incidence was 8.6/1 000 person-years (PY); with 5.4/1 000 PY for AD. The

incidence increased with age, and continued to rise after age 90. Life-time risk was around 20%, with a trend towards increased risk with age that was only significant in men. In comparison, the Framingham study reported similar incidences, which were doubled in the Rotterdam study.[135] Until the incidence from the second cohort is analyzed, the Zaragoza study can only offer indirect prevalence-based measures of changes in incidence.

Secular improvements in management of cardiovascular risk factors could justify this possible decrease in dementia incidence. The fact that both the studies in Stockholm and Zaragoza find reduced risk among men is revealing.[131, 134] Initial efforts to counter cardiovascular diseases in the 70s and 80s focused on men, who then bore the brunt of cardiovascular conditions.[136] It is possible that cardiovascular risk factors have been under-diagnosed and undertreated among women for a significant proportion of the last three decades.[136] More recently, increased focus on women's cardiovascular health might have reversed this trend. If so, we can expect a further reduction in dementia risk in the future, also among women.

Recently, an inverse correlation between risk of neoplasm and dementia has been described.[137] Even relatively benign conditions such as nonmelanoma skin cancer are associated with decreased risk of dementia.[138] Cancer and dementia are both associated with old age, and might represent different pathological mechanisms in the way bodies combat aging.

Sex has a crucial effect in the prevalence of dementia. Men display 19-29% lower prevalence, and this gender gap increases with age, indicating an interaction between age and gender.[128] All these factors need to be considered when planning resources for patients in the future.

1.9 PUBLIC HEALTH PLANNING AND ECONOMICS

The global increase in dementia prevalence places a burden on health care workers, families, policy-makers and societies to improve care and support for affected individuals. Access and quality of care is extremely uneven even within industrialized nations. Access to neurological care can be influenced by availability of services, public perception, costs, and health care policies. For example, Medicare reimbursement policies in the US could be to blame for low prevalence of neurological care for neurodegenerative conditions.[139] In Europe, the estimated cost of dementia reached a total of just over 105 billion euros in 2010, constituting a major economic health challenge in all countries.[140] On average, the per-patient direct health costs rose to 2 673 €, while indirect costs were 13 911 € or over 80% of the total expense. The *per capita* cost of all brain disorders in Spain was 1 592 €, while it was 1 882 € in Sweden.[140] In dementia, direct non-medical costs are responsible for more than 80% of the total expenditure.[140] WHO data indicates that the total cost of dementia as a proportion of country gross domestic product (GDP) ranges from 0.24% in low-income countries to 1.24% for high income countries.[141]

1.10 MORTALITY IN DEMENTIA

Dementia is widely recognized as a cause of reduced life-expectancy, although the effects of factors that contribute to this excess mortality remain under contention.[142-152] Age, sex, baseline cognition, residential setting, comorbidity and dementia diagnosis have all been identified as possible confounders or contributors to death.

1.10.1 Age and mortality

Higher age increases mortality after a dementia diagnoses,[143, 150, 153-155] although younger subjects loose more years of life to the disease.[142] When compared to same-age controls, patients with early-onset dementia presented a hazard ratio (HR) of mortality of 43, while the HR for the older cohort was 3.4.[156] This trend continues among the oldest

old: as mortality rates for the non-demented population raise exponentially, the relative excess hazard due to dementia decreases.[148, 157, 158] Despite this, most studies still find differences in survival between demented and non-demented individuals, even among the oldest old.[148]

Dementia diagnosis differs between the young-onset and late-onset groups, so this must be taken into account when attributing death risk to age.[156] FTD, which typically has earlier onset, presents with higher mortality than other dementia types,[146, 156] particularly when it is associated with MND.[159] Also, comorbidites such as diabetes could be associated to earlier onset of dementia and are also independently responsible for mortality.[160] This effect could be particularly important in younger patients, becoming relatively attenuated with age.[160]

1.10.2 Sex and mortality

Most studies have reported lower mortality rates in dementia in women than in men.[143, 146, 150, 152-154, 157, 161-164] There are exceptions to this trend,[155, 165] with some studies finding different effects of sex depending on dementia type[142, 158, 166, 167] with women afflicted with VaD[166] or LBD[168] faring worse. Because of higher dementia prevalence and lower baseline mortality, women suffer a higher proportion of deaths due to dementia.[124, 132-134] As discussed above with younger patients, since women have lower baseline mortality risks, their mortality hazard when compared to sex matched controls is greater than in men, although they still present lower non-adjusted mortality rates when compared to men.[158]

1.10.3 Cognitive performance and mortality

The effect of baseline cognition on mortality is unclear, with some studies finding increased mortality with advanced but not initial cognitive impairment,[157] others finding increased mortality even with mild dementia,[169, 170] while others fail to demonstrate a

difference relative to initial impairment[154] or speed of cognitive deterioration after diagnosis.[163]

1.10.4 Neuropathology and mortality

The association of several different pathologies upon autopsy is correlated with decreased survival.[151] AD pathology in patients diagnosed with LBD or PDD decreases survival,[171] while AD patients who present with some LB pathology also have worse disease course.[172]

The location and extension of the pathology is also important. In FTD, abundant pathology of any sort in the basal ganglia and anterior cingulate was correlated with shorter survival, as did tau-positive pathology,[173] while others have found tau-negative pathology associated with shorter survival.[174] These discrepancies may be due to the composition of cohorts, where a large proportion of patients with tau-negative FTD with MND or tau-positive with Pick disease or corticobasal degeneration might skew results in one direction or the other.[173] In one study, patients with 4-repeat tauopathies (4R) had significantly shorter disease duration that patients with 3-repeat tauopathies (3R) and, among the bvFTD, apathy was more common in the 4R group.[175]

1.10.5 Dementia type and mortality

Most studies either fail to demonstrate a statistically significant difference in survival between dementia diagnoses[154, 161, 169, 170, 176] or report lower mortality risk with AD.[142, 146, 150] Previous research has focused on AD and VaD, where there is abundant information on mortality, but direct comparisons between cohorts with a range of diagnoses are lacking.[142] Most have compared AD and VaD, sometimes including mixed dementia[150, 161, 166, 169, 177, 178] In these, AD tends to have the more favorable prognosis[158, 162], with mixed dementia sometimes having intermediate risk between AD and VaD, in line with its presumed etiology as a combination of those two conditions.[166] Others compare AD with DLB,[148, 165, 167, 179, 180] with DLB usually presenting higher mortality

risk,[167, 179] with excess risk remaining after controlling for cognitive level.[165] Studies comparing other dementia types are rarer. DLB could be more lethal than PDD,[171] which itself presents higher mortality than PD or controls.[181] Survival in FTD can range from 3 to 9.5 years,[73,93, 159, 175] depending on variant type,[93, 182] presence of MND,[159] presence and type of tau,[154, 159, 174] and symptoms at onset,[93] and compares unfavorably with other dementias.[146, 183].

Most previous studies have compared two,[150, 157, 171, 179, 183] or at most three diagnoses.[161, 166, 170] Two clinic-based studies[146, 156] and one population-based study included more dementia types.[176] Of these, the population-based study only included AD, VaD, DLB and combined dementias and did not find statistically significant differences, probably due to the low number of dementia cases, particularly for DLB (n=12).[176] One of the clinic-based studies also did not find significant differences. The other, by Steenland et al,[146] is more illuminating. The study included specialist clinic patients with a diagnosis of FTD, MND, AD, PD (with and without dementia), DLB, MCI and controls. Highest mortality was found with MND, followed by FTD, DLB, PD, AD and MCI, with this last group of patients still exhibiting significant excess mortality relative to controls.

The origin of these disparities might lie in the particular neurodegenerative background of each of these conditions, but other factors need to be considered. VaD and mixed dementia are etiologically associated with cardiovascular risk factors. Cardiovascular mortality has been reported the first cause of death across dementia cohorts,[169] so it stands to reason that these conditions would present with higher mortality. Coexisting conditions, such as MND in FTD, would naturally drive up mortality. The type of cognitive impairment might play a role, with behavioral problems present in FTD and DLB perhaps threatening survival more than mnestic decline. Additionally, the management of these behavioral problems might result in additional mortality: neuroleptics have been associated with excess mortality, as has institutionalization, although in both cases it is difficult to tease apart cause and effect. The psychological profile of different dementia types might make some more available to

social support than others: AD patients are said to lose their "social graces" later in the disease process, making them relatively easier to care for at least in earlier stages. By contrast, FTD patients can display disturbing psychological features from onset and can behave unpredictably and be intractable to care. Other accompanying symptoms may be relevant. Autonomic dysfunction and its severity was associated to reduced survival in DLB and PDD,[184] while hallucinations at disease-onset also appear to worsen prognosis.[171] Language-deficits in bvFTD are associated with worse prognosis.[93] Whether this is due to neurobiological reasons or heightened difficulties in communication and care is impossible to know.

1.10.6 Body-mass index and mortality

BMI is a useful biometric measure and predicts mortality in a number of populations.[95, 185] The normal range as defined by the WHO spans from 18.5 to 24.9 kg/m^2,[95] and is associated with lower mortality among younger adults – the population among which the index was originally developed.[102] The optimal range for older adults and other special populations is less clear. Cut points between 19 and 23 have been proposed to guide nutritional screening in older populations,[185-188] and many studies propose that the optimal weight for lowest mortality might lie in the overweight range as defined by the WHO (25-29.9 kg/m^2) or even the beginning of the obese weight range (over 30 kg/m^2). [189-191] This finding of excess weight, traditionally considered detrimental to health, as being protective in older adults has been termed the "obesity paradox"[192] and mirrors findings from studies of other cardiovascular risk factors. Indeed, dislipidemia, high blood pressure, high body-fat,[193] or altered homocysteine, creatinine, and parathyroid hormone concentrations have been associated with lower mortality in some populations giving rise to the "reverse epidemiology hypothesis".[194] This is a phenomenon that is often apparent from epidemiological studies, but it is unclear whether it reflects an actual biological effect or whether it is the result of biases and confounding.

On the one hand, a survival effect needs to be considered: persons presenting these risk factors may have lower probabilities of reaching the point of inclusion in

epidemiological studies. Thus, the persons who are included are statistical oddities, reflecting tenacious constitutions or other factors that counter the cardiovascular risk factors that they present. Over-adjustment for comorbidity might also be a problem: since cardiovascular risk factors directly cause comorbidity, excessively controlling for said comorbidity might artificially reduce or eliminate the deleterious effect linked to said factors.[195] Others contend that it is rather the extreme values on the low end of the spectrum of certain cardiovascular risk factors that might be associated with higher mortality: thus, it is low blood pressure below the normal range that would be associated with mortality and would drive the statistical findings. In one study, obese patients were younger, with stronger handgrip and better ability to walk, and reported less anorexia and feeding problems than patients from other weight categories.[196] This reinforces the importance of adequately exploring the distribution of a sample throughout the widest possible range of values in order to detect a U or J shaped distribution. Time discrepancies between competitive risk factors could mediate this phenomenon.[197] In cholesterol levels, blood pressure and BMI, the lowest values in the spectrum represent immediately life-threatening conditions, and would overwhelm the excess risk found at the higher end of the spectrum.[198, 199] Finally, reverse causation might account for the observation, if the underlying cause and not the factor itself, were responsible for excess mortality. This could occur, for example, in the case of cardiac pump failure in a patient with low or normal blood pressure.[197]

On the other hand, most studies include different risk groups for a given factor and replicate the reverse epidemiology effect. Also interesting are the populations in which this effect has been described, which range from older populations,[190, 200, 201] to patients suffering from renal failure,[198, 202] established cardiovascular disease,[193, 203] heart failure,[197, 204] stroke,[205] chronic obstructive lung disease,[193] rheumatoid arthritis,[193] malignancies and acquired immunodeficiency síndrome (AIDS).[203] Although outwardly different, these groups share some common characteristics. First, they all present with shortened life-expectancies, in which the effects of traditional cardiovascular risk factors might not have time to materialize.[203, 206] Second, most represent catabolic states[193] where malnutrition is a frequent problem and directly linked to mortality: if the risk associated with malnutrition was much greater than that associated with traditional cardiovascular

risk factors, patients with higher blood pressure, cholesterol and BMI would have better nutritional reserve and better survival, even at the expense of increased cardiovascular risk. However, cardiovascular mortality remains among the first causes of death in these populations.[169] This may be accounted for by a third factor: inflammation. Frequently linked to malnutrition, inflammation is part of the malnutrition-inflammation complex syndrome (MICS) described among terminal renal failure patients[198] but could also be applicable to other populations, such as patients with heart failure.[197] Chronic inflammation leads to decline in appetite, muscle and fat wasting, hypercatabolism, endothelial damage, reduced high-density lipoproteins (HDL) and increase in oxidized low-density lipoproteins (LDL), and atherosclerosis.[195, 198] Together, these mechanisms explain the two main causes of death among these special populations: infectious and cardiovascular. Indeed, MICS has been blamed for the excess cardiovascular disease found among renal failure patients and much attention is being devoted to chronic inflammation as a cause for cardiovascular disease.[207] The interest in periodontal disease and C-reactive protein,[207] as linked to cardiovascular disease[198] is testimony to this. Indeed, in a study examining the association between cholesterol level and mortality in dialysis patients, a reverse epidemiology phenomenon was observed only in those in which MISC was evident, while the normal epidemiological observation of higher cholesterol linked to higher mortality appeared in patients who did not have MICS.[208]

A given factor could have competing effects: high creatinine is a marker of reduced renal function, but also of high muscle mass and meat intake. In patients on dialysis, glomerular filtration is already so low that fluctuations in creatinine can be accounted for by the other two factors, making it a better marker of good nutritional status than of renal function.[194]

Although the impact of cardiovascular risk factors has been less studied in dementia, the characteristics of this syndrome make it a prime candidate for reverse epidemiology.[199] Dementia presents shortened life expectancy where malnutrition is a contributing factor for death. Subjects with dementia present, on average, lower BMI than

their peers, and lower BMI has been correlated to increased mortality and severity of cognitive impairment.[209-211]

Reverse epidemiology observations are in stark contrast with a large body of studies supporting the treatment of cardiovascular diseases even in the populations in which this effect is typically described. In a study on treatment of hypercholesterolemia with statins among diabetic patients on dialysis, no effect was found on cardiovascular death, but there was a reduction in cardiac events.[195]

This may be a paradox, but only superficially. Part of the confusion may stem from the term "reverse epidemiology", which seems to imply that there is something abnormal about these observations. As Port put it in a recent article criticizing the term: *"Epidemiology is not reversed. There is nothing wrong with epidemiology. It is the true epidemiology of observational studies that led to clinically relevant findings that are specific to dialysis patients".*[195] The term "phenomenon of altered risk factor patterns" or "risk factor reversal"[194] has been proposed instead. Both proponents and detractors of reverse epidemiology agree in substance: the conclusions should not be that high blood pressure, high cholesterol or high adiposity are beneficial[195] and neither should the treatment of cardiovascular risk factors be abandoned, although new goals might need to be developed in these groups.[195] Rather, cardiovascular risk factors remain risk factors but identify patient subgroups which are more exposed to other, more deadly, risk factors. Hence, the course of action is not to stop treating obesity in all populations, but to identify the factors, such as malnutrition and inflammation, responsible for the higher mortality detected among thinner patients.

1.11 SVEDEM: THE SWEDISH DEMENTIA REGISTRY

SveDem, the Swedish Dementia Registry, www.svedem.se, was created in 2007 following an initiative of the Swedish Brain Power network of researchers and is funded through the Swedish Association of Local Authorities and Regions (*Sveriges Kommuner och Landsting*) and the Swedish Brain Power.[212-216] Its aim is to evaluate and improve quality and equality of care for patients with dementia throughout Sweden.[217] Newly diagnosed patients with dementia are included in the web-based registry, which provides a framework for recording aspects of diagnostic workup,[214, 215, 218] treatment and care.[213] The registry is active throughout the country.[219] Both specialized memory clinics and primary care centers contribute patients to SveDem although coverage varies greatly between these two types of units. During 2011, the percentage of patients evaluated at specialized memory centers which were included in SveDem rose to 90%,[217] reached 94% by 2012[212] and 95% 2013[219]. Although the number of primary care centers connected to the registry rose by 45% in 2011, SveDem coverage for patients diagnosed in these types of units remains much lower than for specialist clinics: it was 67% of all primary care centers in 2012.[212] Population-based calculations from the Swedish Board of health and welfare (Socialstyrelsen) estimate around 24,000 new dementia cases in Sweden per year,[220] which would imply that SveDem, with 4 941 new entries during 2011, has a coverage of 25% of all new dementia diagnoses made nationwide. The coverage in 2013 with approx 8 000 entries is 35%. This gap between expected incidence and registration can be attributed to several factors. First, expected incidence is a calculation, and may be higher or lower than reality. Second, a number of incident cases may be missed due to late diagnosis or absence of diagnosis. According to the WHO, late and absent diagnosis is a world-wide problem,[221] and there is no reason to believe Sweden should be an exception. Third, the uneven coverage in primary centers may be responsible for a substantial percentage of missing patients; enhancing coverage in all types of units is one of the developmental priorities of SveDem.[220]

Patients are included in SveDem at the time of incident dementia diagnosis using ICD-10 criteria and are followed annually.[213] Dementia diagnoses are coded as dementia

with AD, VaD, mixed AD and VaD (mixed), DLB, PDD, FTD, unspecified dementia (where specific dementia diagnosis is not ascertained) and other dementia types (grouping miscellaneous dementia disorders such as corticobasal degeneration, Creutzfeldt-Jakob or alcohol related dementias).[213] In addition to ICD-10 criteria[5], the McKeith criteria[13] are employed for LBD, the Manchester-Lund criteria for FTD[12] and Movement Disorder Society Task Force criteria for PDD.[10] Variables recorded at the time of registration include age, gender, baseline MMSE, co-residency status (co-residing vs. living alone), residential setting, work status, driving status, weapon licence and permits, and biometric data (height and weight). The number of medication that the patient takes regularly at the beginning of diagnostic workup comprises all medications that the patient takes that appear in the official Swedish Drug Index[222] and is included as a variable. This variable is used as a proxy for comorbidity,[213,223] since it has been shown to be better than other medication-based comorbidity scores at predicting morbimortality.[223] The presence of cardiovascular medication, antidepressants, antianxiety medication, neuroleptics and sleeping aids is recorded. Cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) antagonists at baseline and again upon diagnosis are entered.

After diagnosis, additional variables are included such as number of medication after the diagnostic process, introduction of cholinesterase inhibitors and NMDA medication and treatment with vascular medication, antidepressants, neuroleptics, sleeping aids and antianxiety medication after diagnosis.[224] Social interventions such as negotiation for termination of driving with the patient and their family, removal of driving or weapon licenses, or referrals for social support or legal guardianship are noted.[213, 215, 217] Annual follow-up includes a revision in any changes in any of the abovementioned variables. The proportion of patients whose diagnoses change in these follow-up visits is low, around 5% for the whole register.[217] The highest percentage of changing diagnoses occurs in the "unspecified" diagnosis (15%) while change in diagnosis in the AD group occurs in only 3% of cases. SveDem is collated monthly with the national population registry so that deceased patients are withdrawn from the follow-up schedule and a date of death is entered.[225]

The regional ethics committee of Stockholm approved the creation and data management of SveDem. SveDem studies have been approved by the regional ethics commitees of Stockholm. At the time of work-up, patients and caregivers are informed orally and in writing about SveDem and can refuse to participate. There are procedures for withdrawal requests. Data is anonymized and analyzed off-site. The online database and information technology support is carried out by the Uppsala Clinical Trial Center.[213] A coordinator routinely selects 10% of medical records from each unit to validate the data. Each participating unit has access to descriptive online statistics of their registrations and comparisons with data from the region and from all SveDem.

SveDem aims to integrate seamlessly into the overarching organization of Swedish dementia care and become a valuable tool. Clinics can directly obtain data on their own statistics and check them against regional and national averages. This allows resource planners and practitioners to compare their diagnostic times and the types of ancillary testing they perform against others operating in comparable or different settings.[225, 226] In some instances, such statistics have revealed easily-solved problems: in one case, one unit realized that their diagnostic times were the longest in the country. They solved it by scheduling testing and the second visit directly after the first interview, which put their diagnostic delay on par with other units. SveDem operates within the highly decentralized Swedish healthcare system: elderly care and finance in each area is managed by the 290 municipalities while health care and finance is managed by 21 counties.[217, 227]

In 2010, the Swedish National Board of Health and Welfare introduced a framework for the management and care of persons with dementia.[228] National indicators were developed for evaluation of dementia care. Seven of these indicators can be evaluated using SveDem. One such indicator is the proportion of patients with a basic diagnostic work-up as a base for the dementia diagnose. A basic diagnostic work-up is defined and recommended to all patients suspected of dementia. This work-up includes a structured clinical interview, an interview with a knowledgeable person close to the patient, an evaluation of the physical and psychological situation of the patient, cognitive

testing with, at minimum, MMSE and clock test, cerebral imaging and blood analyses including calcium, homocystein and thyroid function. SveDem´s own goal is that >90 % of patients diagnosed with dementia whoud have a basic dementia work-up performed.[212, 217] This work-up can be expanded, if necessary, depending on available testing at the discretion of the specialist.[228] The guidelines further stress the importance of early diagnosis and attention to social aspects of the disease.

Furthermore, primary care plays an important role in dementia care in Sweden. Primary care physicians diagnose a large number of cases, are capable of prescribing medication for dementia and independent of specialists in many cases. In certain instances, such as when a patient is under 65 or the diagnosis is difficult, patients can be referred from primary to specialist care. Conformity with these national guidelines is an important quality marker which SveDem is in a unique position to assess.[229] A recent study on AD patients within SveDem showed that 85% of patients diagnosed in specialist care and 61% of those diagnosed in primary care complete this basic diagnostic work-up.[227] Clock-test and CT were the required examinations less-often performed in primary care. Table 13 shows the percentages of each diagnostic test in specialist and primary care.

SveDem is a phenomenal research tool and cross-linkage possibilities with other registries are being explored.[230, 231]

Table 13. Diagnostic work-up frequencies in specialist and primary care and comparisons between them*

	Specialist care (n=2812)	Primary care (n=1215)	p-value
Full basic examination, no. (%)	2333 (85.1%)	659 (60.7%)	<0.001†
No. of basic tests, mean (SD)	3.83 (0.43)	3.48 (0.74)	<0.001‡
MMSE, no. (%)	2731 (96.4%)	1141 (94.9%)	<0.001†
CT, no. (%)	2593 (92.8%)	934 (80.6%)	<0.001†
MRI, no. (%)	444 (16%)	27 (2.4%)	<0.001†
Brain imaging (CT or MRI) no. (%)	2705 (97.8%)	902 (81.1%)	<0.001†
LP, no. (%)	1488 (53.3%)	50 (4.4%)	<0.001†
Isotope examination, no. (%)	322 (11.6%)	13 (1.1%)	<0.001†
EEG, no. (%)	367 (13.2%)	6 (0.5%)	<0.001†
Assessment by occupational therapist, no. (%)	1160 (41.5%)	301 (26.5%)	<0.001†
Assessment by physiotherapist, no. (%)	133 (4.8%)	115 (10.2%)	<0.001†
Assessment by speech therapist, no. (%)	93 (3.3%)	102 (9%)	<0.001†
Neuropsychological test, no. (%)	796 (28.5%)	36 (3.2%)	<0.001†
Total no. of tests mean (SD)	5.55 (1.31)	3.9 (1.17)	<0.001‡
No. of days between initial date and diagnosis date mean (SD, median)	88 (139, 58)	133 (239, 62)	<0.001‡

CT: computed tomography. EEG: electroencephalography. LP: lumbar puncture. MMSE: Mini-mental State Examination. MRI: magnetic resonance imaging. no. : number of patients. SD: standard deviation.

*Reproduced with permission from Ingrid Nilsson-Modéer *Diagnosis and treatment of Alzheimer´s disease in specialist units compared to primary care*. (Unpublished master´s thesis. Department of Neurobiology, Care Sciences and Society, Study program in Medicine. Karolinska University, 2013) p. 15.
† Pearson's Chi-square ‡Independent t-sample test.

Abbreviations: Full basic examination refers to guidelines by the Swedish National Board of Health and Welfare (Socialstyrelsen) which include structured clinical interview and physical examination, cognitive testing including, at minimum MMSE and clock test, cerebral imaging and basic blood analyses.

2. OBJECTIVES

2.1 STUDY I

1. To describe the baseline clinical and paraclinical characteristics of patients diagnosed with subjective cognitive impairment (SCI) in a memory clinic, and to compare them with those of patients diagnosed with mild cognitive impairment (MCI) and Alzheimer's disease (AD).
2. To determine which factors contribute to an SCI, MCI or AD diagnosis.

2.2 STUDY II

1. To describe the baseline characteristics of a large national cohort of incident dementia patients.
2. To determine the relative mortality risks of different dementia disorders.
3. To examine mortality risk in relation to age, sex, baseline cognitive performance, number of medication, institutionalization and coresidency status in patients with dementia.

2.3 STUDY III

1. To determine the body mass index (BMI) range corresponding to lowest mortality risk in patients with dementia.
2. To determine whether the BMI associated with lowest mortality is different in women and in men, or in different age groups.

3. HYPOTHESES

3.1 STUDY I

1. Individuals with subjective cognitive impairment (SCI) differ from those with mild cognitive impairment (MCI) or Alzheimer's disease (AD) in baseline characteristics.
2. SCI subjects are younger and have better cognition and lower frequency of cardiovascular risk factors than patients with MCI or AD.
3. Psychiatric comorbidity is more prevalent among SCI individuals.
4. SCI individuals have less cerebral atrophy than MCI or AD patients
5. The prevalence of apolipoprotein E4 (ApoE4) is lower among SCI than among AD or MCI patients.
6. AD cerebrospinal fluid (CSF) biomarker patterns are more infrequent within the SCI group.

3.2 STUDY II

1. AD type dementia is associated with lower mortality risk than other dementia types.
2. Higher age is associated with increased mortality risk in both genders and all dementia disorders.
3. Male sex is associated with increased mortality risk.
4. Low cognitive level measured by the Mini Mental State Examination (MMSE) is associated with higher mortality risk.
5. Higher comorbidity, measured as number of habitual medication at the time of diagnosis, is associated with higher mortality risk.
6. Living in an institution is associated with higher mortality risk.
7. Living alone is associated with higher mortality risk.

3.3 STUDY III

1. In patients with dementia, the distribution of body mass index (BMI) by mortality risk follows a U shaped curve with the point of minimum mortality occurring in the normal or overweight BMI range.
2. Excess mortality risk is present in obese individuals (BMI $\geq$30 kg/m^2).
3. The BMI range associated with lowest mortality risk is different in women than in men.

4. METHODS

4.1 STUDY I

Study I is based on the Karolinska Memory Clinic database. Methods for this study are described in depth in the patients and methods section of the article. What follows is a quick overview.

4.1.1 The Karolinska Memory Clinic

The Karolinska Memory Clinic is part of the Department of Geriatric Medicine at Karolinska University Hospital, Huddinge, and evaluates around 450 new patients each year referred due to cognitive problems Diagnostic work-up is made within a clinical framework that includes a team of geriatricians, psychiatrists, neurologists, neuropsychologists, nurses, occupational therapists, speech therapists and social workers. Neuroimaging and CSF markers are often available to supplementary data from routine clinical work-up.

All patients receive a physical examination, cognitive screening, patient interview and clinical assessment, with further testing when necessary. An in-depth neuropsychological examination is performed, with patients evaluated with MMSE and a combination of other tests, including items from Wechsler Adult Intelligence Scale, Revised (WAIS-R),[232] different tests for memory,[233-235] Trail making tests,[233] and/or Verbal Fluency test (FAS).[236] Diagnosis conforms to current best practice and is made by a multidisciplinary panel, using the diagnostic criteria valid at the time for each entity. The present study contains patient data from 2007 through 2009. During this period, the diagnosis of SCI conformed to the ICD-10 classification "Z03.3 = observation for possible neuro-organic disorder" (ICD-10) when patients described memory complaints that could not be objectively verified[5]. The MCI diagnosis followed the consensus criteria for MCI,[237] The ICD-10/DSM-IV (Diagnostic Statistic Manual, 4th edition) criteria for dementia, and the NINCDS-ADRDA criteria were used for AD.[5, 238, 239]

In study number I, patients diagnosed at the Karolinska Memory Clinic were retrospectively identified and included. From 2007 through 2009, 1 154 patients had been diagnosed. Diagnoses other than AD, MCI or SCI were excluded. Additionally, patients with severe comorbidities that put in question the diagnosis (such as cerebral tumors, concurrent epilepsy or metastasis) were also excluded. However, common somatic or psychiatric comorbidities, such as depression, anxiety and heart or kidney failure were not excluded. In total, 993 patients were included.

All patients had neuroimaging and 560 had data on blinded medial temporal lobe atrophy rating (MTA) following the Sheltens scale[240]. In 943 patients, white matter lesions (WML) on axial C or fluid attenuation inversion recovery (FLAIR)-sequence MRI were graded following a revised Fazekas scale.[241] Central atrophy was graded in 980 patients (for details, please refer to the neuroimaging section in methods of article I).

CSF was available for 744 patients, and cut-points were set at 400 ng/l or higher for total tau (t-tau), 80 ng/l or higher for phosphorylated tau (p-tau) and 450 ng/l and under for Aβ 42. ApoE genotyping was available for 325 patients. Neuropsychological testing is described in the corresponding section in methods of article I. Briefly, patients were assessed with the Mini-Mental State Examination (MMSE) together with other tests, selected according to the patient´s clinical picture. Behavioral and psychological symptoms associated with dementia (BPSD) were also noted, together with depression, evaluated through interview and with the Cornell Scale for Depression in Dementia (CSDD)[242] with 8 as cut-point, where a score of 8 or more indicates depression.

The regional ethics committee in Stockholm approved this study.

4.1.2 Statistical methods

Discrete variable group differences were compared with χ^2-tests. When means were non-normal, p-values from logistic regression were used. MCI and AD group means were compared to those of the SCI group.

The second part of the article employs a statistical model to analyze the similarities between each patient in the database and an "AD type" as defined by the AD group. In order to do so, a statistical model was created in three phases. First, a number of variables were tested together to find which combination accurately classified the patients in our sample into AD/not AD (where "not AD" included MCI and SCI patients). The best variables proved to be age, sex, MMSE, Aβ42/t-tau quotient, and p-tau. The logistic regression model combining those classified 94.9% of the sample correctly. In the second stage, the model was applied to every patient, assigning each individual a probability of being more "AD-like" (henceforth refered to as "AD-likelihood"). These probabilities were stored as a variable and used as outcomes for the next stage. In this last third stage, separate models for MCI and SCI were run, using AD-likelihood as outcome. Then, each clinical variable was entered one by one, in order to identify which increased the probability of being classified as AD by the model. The statistical methods section of article I contains more details.

4.2 STUDIES II AND III

A succinct review of the methods of articles II and III follows; for more information, the reader is referred to the methods section of the corresponding article.

4.2.1 The SveDem dementia registry

Studies II and III employ data from SveDem – the Swedish Dementia Registry – which registers incident dementia cases nationwide. These studies include patients

registered from 2008 through 2011 in specialist memory clinics. Primary care was excluded due to later and more irregular inclusion of those units into the registry, uncertainty over national coverage levels and differences in diagnostic processes compared to specialist care as has been shown in a number of studies based on SveDem and as is apparent in table 13.[214] Study II and III are based on inclusion of 15 224 patients. In study II patients were excluded if they had incomplete data on dementia diagnosis, age, sex and survival: 15 patients (0.1%) were missing this data, leaving 15 209 patients available for analysis. In study III patients were excluded if they had incomplete data on dementia diagnosis, age, sex, survival and BMI: 11 398 remained for analyses.

Variables examined in both these studies include age, sex, dementia diagnosis, baseline MMSE, coresidency status (living alone vs cohabiting), residential setting (at home, nursing home or a special institution for persons with dementia). Medication was considered: number of medication (as a proxy for comorbidity[213 223]), as well as presence or absence of cardiovascular medication, antidepressants, antianxiety, neuroleptics and sleeping aids was examined. Cholinesterase inhibitors and NMDA antagonists prescribed upon diagnosis were entered. BMI was examined as a possible confounder in study II and was the main focus variable in study III.

4.2.2 Study II

Cox proportional hazards regression models were used to identify factors associated with mortality risk. Results are presented as HR of death with 95% confidence intervals (CI). The assumption of proportionality of hazards was tested with Kaplan-Meier survival curves and time-dependent covariates: in instances in which this assumption was violated, HRs were calculated at the beginning of the observation period and at day 1 000 of follow-up. Means and and standard deviations (SD) were calculated for descriptive statistics.

Crude, age- and sex-adjusted, age-, sex- and medication-adjusted models were calculated. The fully adjusted model included age (entered as a categorical variable with cut-ponts at 65, 75, and 85 years), number of medication (in categories 0-1, 2-5, 6-9 and 10 or more) and MMSE (missing, not assessable, 0-9 points, 10-19 points, 20 to 24, and 25 and over). The model also included place of residence classified in patients living at home, or in an institution, sex and whether the patient lived alone. Dementia was included in the final model in eight categories: AD, mixed, VaD, DLB, FTD, PDD, unspecified and other.

4.2.3 Study III

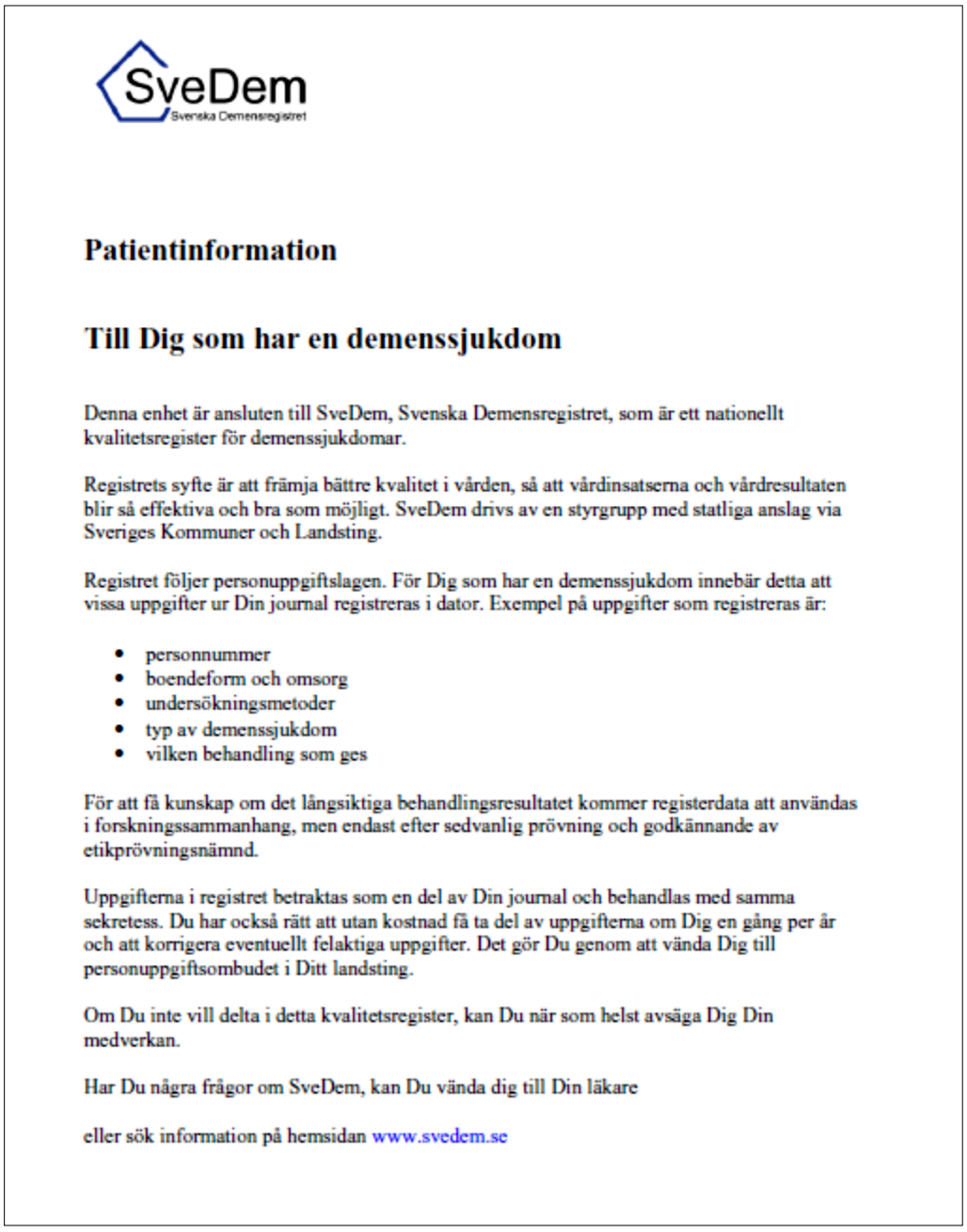
Statistical methods were similar to study II and details can be found in the methods section of study II, so we will focus here only on the particularities of this study.

BMI was explored in categories following WHO guidelines: underweight (BMI under 18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (over 30 kg/m^2). Since previous studies showed that excess risk could be present also in thinner normal-weight older adults[185-187] an additional WHO cut-point was used ("slim" individuals from 18.5 to 22.9).

Piecewise linear representation variables (splines) were introduced in this article in order to best represent the distribution of BMI and mortality. Splines are concatenated variables separated by cut-points (or knots) that are chosen by the researcher. In this case, linear splines were used, meaning that BMI was a continuous variable, and that the relationship between BMI and mortality risk was considered to be linear within each segment. Different knots were tested and stratified analyses for sex and age groups were also undertaken.

4.2.4 Ethics

At the time of work-up, patients and caregivers are informed orally and/or in writing about SveDem, and can refuse participation. Withrawal of consent is available by contacting SveDem and requesting removal of the patient´s data. Further information is available on the SveDem website at www.svedem.se. Research projects using SveDem data need ethical approval. Thus, study II and III were approved by the regional ethics commitees of Stockholm (approval number 2009/209-31). Figure 1 shows the abridged patient information that is displayed in units that are linked to SveDem. Additional written and verbal information is given to patients. Data is anonymized and analyzed off-site.



SveDem
Svenska Demensregistret

Patientinformation

Till Dig som har en demenssjukdom

Denna enhet är ansluten till SveDem, Svenska Demensregistret, som är ett nationellt kvalitetsregister för demenssjukdomar.

Registrets syfte är att främja bättre kvalitet i vården, så att vårdinsatserna och vårdresultaten blir så effektiva och bra som möjligt. SveDem drivs av en styrgrupp med statliga anslag via Sveriges Kommuner och Landsting.

Registret följer personuppgiftslagen. För Dig som har en demenssjukdom innebär detta att vissa uppgifter ur Din journal registreras i dator. Exempel på uppgifter som registreras är:

- personnummer
- boendeform och omsorg
- undersökningsmetoder
- typ av demenssjukdom
- vilken behandling som ges

För att få kunskap om det långsiktiga behandlingsresultatet kommer registerdata att användas i forskningssammanhang, men endast efter sedvanlig prövning och godkännande av etikprövningsnämnd.

Uppgifterna i registret betraktas som en del av Din journal och behandlas med samma sekretess. Du har också rätt att utan kostnad få ta del av uppgifterna om Dig en gång per år och att korrigera eventuellt felaktiga uppgifter. Det gör Du genom att vända Dig till personuppgiftsombudet i Ditt landsting.

Om Du inte vill delta i detta kvalitetsregister, kan Du när som helst avsäga Dig Din medverkan.

Har Du några frågor om SveDem, kan Du vända dig till Din läkare

eller sök information på hemsidan www.svedem.se

Figure 1. Abridged information on SveDem to be displayed in all units linked to the registry. Reproduced with permission.

Translation.

"To you who have been diagnosed with dementia: This unit is linked to SveDem, the Swedish Dementia Registry, which is a national quality registry for dementia diseases. The objective of the registry is to support increased quality of care, so that care interventions and patient outcomes are as effective and favorable as possible.

SveDem is directed by a steering commitee and receives state funds through the Swedish association of local authorities and regions. The register follows the law on personal data. For you who have been diagnosed with dementia this implies that some data from your personal history will be registered in a computer. Examples of data which are registered are your personal ID number, residential setting and care, testing methods, type of dementia, treatment. In order to obtain knowledge on long-term treatment results, register data can be used for research, but only after customary approval of ethical committees.

The data in the registry is treated like your personal history, and is guarded with the same secrecy. You also have the right to obtain, once a year and free of cost, the data about you that is available in the registry, and to correct any eventual errors. This you can do by applying to the Personal Data Office in your region. If you do not wish to take part in the registry, you can rescind your participation at any time. If you have questions, please contact your doctor or seek information in our homepage: www.svedem.se"

5. RESULTS

5.1 STUDY I

Detailed results on study I are shown in the article. A brief summary with the most relevant findings follows below.

5.1.1 Descriptive statistics

The number of included patients was 433 with SCI, 373 with mild cognitive impairment (MCI) and 187 with Alzheimer's disease (AD). Descriptive statistics are shown in tables 1-4 of the first article. Demographic differences were evident: SCI patients were younger, with more years of education, better cognition (as evidenced by the MMSE) more likely to be female and have a family history of dementia, and less likely to have cardiovascular risk factors than the other groups. The mean MTA rating in the SCI sample was 0.98 on the right side and 1.00 on the left, significantly less than in the MCI or AD groups and within normal parameters. Likewise, dementia biomarkers in CSF was more likely to be normal in the SCI group and the percentage of patients with ApoE ε4 allele was lower than in the AD group. The average Cornell Scale for Depression in Dementia (CSDD) score for the SCI group was 7.8 (SD 5.8), near the cut-point of 8 which was established for depression. This average was higher than in the AD group (table 2 of article I).

5.1.2 Statistical prediction model

These models calculated the predicted likelihood for the SCI and MCI patients of being "AD-like". Beta-coefficients represent the percentage of difference in this likelihood between the two categories in dichotomous variables, while they represent the percentage difference per unit in continuous variables.

Table 5 of article I shows the results from this model. Arterial hypertension was associated with a 7% increase in AD-likelihood in SCI patients, while results were non-significant for MCI. Stroke or transient ischemic attack (TIA) reduced AD-likelihood in

the MCI group by 26%. Mean MTA increased the AD-likelihood in the SCI group but decreased it among MCIs. WML were associated with reduced AD-likelihood in MCI, but increased in SCI. In conclusion, direct or indirect markers of cardiovascular risk tended to be associated with increased AD-likelihood in the SCI group and reduced AD-likelihood in MCI.

5.2 STUDY II

Of 15209 patients with dementia registered in SveDem, 59 % were women. The average age was 78.1 years (SD 8.2) and the mean MMSE was 21.3 (SD 5.1). Few patients had advanced dementia as measured by MMSE (see table 1 of article II).

Table 2 of article II shows baseline differences between dementia diagnoses. Thirty-seven percent of the sample were diagnosed as AD, and twenty-five percent as mixed dementia. The mean age of diagnosis was 77 (SD 8.3) for AD, but was lower in DLB and FTD and higher in VaD.

Follow-up ranged from 0 to 1 869 days (average 2.5 years), with 37 619 PY at risk and 4 287 deaths (114 deaths/1 000 PY; 95% confidence interval, CI 111-117). Table 1 of the article shows mortality rates according to different baseline characteristics.

Sex- and age-adjusted mortality comparisons between our cohort and the general Swedish population are shown in table 3 of the article. The standardized mortality ratio (SMR) for the cohort was 1.49 (95% CI 1.41-1.58). The increased mortality was higher for younger patients (SMR 12.46; 95% CI 2.58-36.43 in persons between 45 and 54), and for women (SMR 1.84; 95% 1.80-1.98).

HR for death from Cox hazard regressions are shown in table 4 of article II. Time-dependent covariates were included for DLB, unspecified dementia and other dementias because they presented with non-proportional hazards (table 5; article II). In crude and adjusted analyses, men had increased mortality risk compared to women (table 4; article

II). There was no interaction between MMSE and sex, or sex and dementia type. This difference remained when stratifying by dementia disorder, although results were not significant in FTD or LBD (article II).

Before adjusting, each year of age was associated with a risk increase of death of 8%. In adjusted analyses, risk increased with each subsequent age category, was three times higher in 74-84 year group compared to patients under 65 and became six times higher in the group over 85 (table 4; article II).

Using MMSE score 25 and over as reference group, patients scoring lower presented increased risk of death. Patients deemed "not assessable" by MMSE presented the highest risk (HR 3.72, 95% CI 3.19-4.35).

Living in an institution and taking more medications were associated with higher risk (table 4; article II). There was no difference between living alone vs having a coresident.

As can be observed in Kaplan-Meier survival curves included below (figure 2) AD had higher survival rates than other dementias. In non-adjusted Cox regression analyses, the highest HR for mortality appeared for VaD, when comparing to AD which was the reference category (see results section in article II). After adjusting for age and sex, Parkinson's disease dementia (PDD) was the dementia type with highest risk. When medication was introduced into the model, FTD became the dementia type with highest risk (see figure and results in article II).

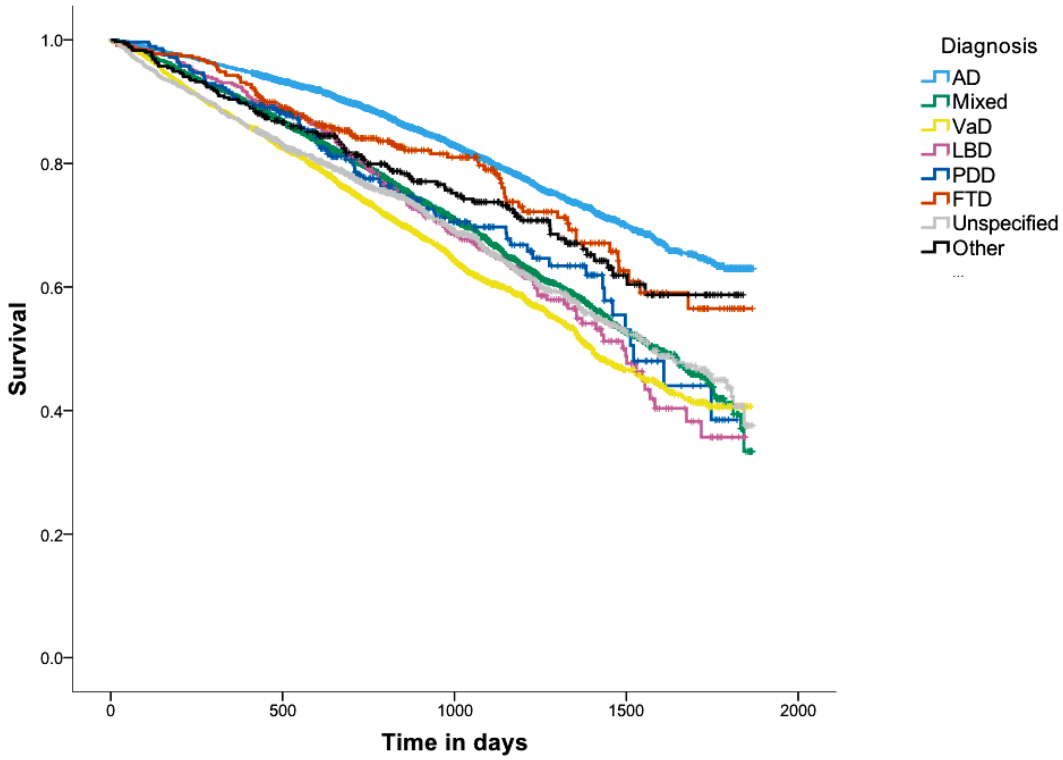


Figure 2. Unadjusted Kaplan-Meier curves for the different dementia diagnoses. Y-axis: estimated survival percentages. X-axis: number of days. When not adjusting for age, patients with Vascular dementia (VaD) has the highest mortality risk. Age-adjusted mortality risk was highest for frontotemporal dementia (FTD). AD: Alzheimers dementia. Mixed: mixed Alzheimer's and vascular dementia. LBD: Lewy body dementia. PDD: Parkinson's disease dementia; Unspecified: unspecified dementia. Other: other dementia diagnoses.

In the final adjusted analysis, all other dementia types were significantly associated with higher mortality risk compared to AD (table 5; article II). FTD demonstrated the highest risk (HR 1.91; 95% CI 1.52-2.39). Mixed dementia presented intermediate risk between AD and VaD. Non-proportional hazards were present in DLB, unspecified dementia and other dementia, meaning that death risk diverged from AD over time. However, the average risk over the whole observation period for DLB was higher than for AD and increased over time (table 5; article II).

Post-hoc analyses were rerun including primary care and the years 2007-2012 which made 28 704 patients available for analyses. As can be seen in table 14 (shown below), HR remained roughly similar to those obtained from the specialist clinic cohort.

Table 14. Comparisons of results from survival analyses between the whole cohort and only specialist clinic patients*

		All patients 2007-2012 N= 28704		Specialist clinics 2008-2011 N=15209	
		HR	p	HR	p
Sex	Women	ref		ref	
	Men	1.56	<0.000	1.56	<0.000
Age					
	<65	ref		ref	
	65-74	1.80	<0.000	1.96	<0.000
	75-84	2.96	<0.000	3.32	<0.000
	≥85	5.38	<0.000	6.17	<0.000
MMSE	≥25	ref		ref	
	20-24	1.47	<0.000	1.45	<0.000
	10 to 19	2.21	<0.000	2.14	<0.000
	0 to 9	3.11	<0.000	2.91	<0.000
	Not assessable	3.47	<0.000	3.72	<0.000
Coresident	No	ref		ref	
	Yes	1.07	0.027	1.02	0.485
Residency	Home	ref		ref	
	Institution	1.54	<0.000	1.42	<0.000
Num. Medication	0-1	ref		ref	
	2 to 5	1.20	<0.000	1.25	<0.000
	6 to 9	1.36	<0.000	1.53	<0.000
	≥10	2.19	<0.000	2.14	<0.000

Dementia type	AD	ref		ref	
	Mixed	1.44	<0.000	1.33	<0.000
	VaD	1.52	<0.000	1.56	<0.000
	PDD	1.70	<0.000	1.47	<0.000
	FTD	2.12	<0.000	1.91	<0.000
	DLB average	1.76	<0.000	1.75	<0.000
	DLB at beginning	1.31	0.079	1.23	0.211
	DLB at day 1000	2.02	<0.000	1.89	<0.000
	Unspecified average	1.02	0.598	1.42	<0.000
	Unspecified at beginning	1.21	0.002	1.75	<0.000
	Unspecified at day 1000	0.929	0.137	1.28	<0.000
	Other average	1.22	0.028		
	Other beginning	1.56	<0.000	1.92	<0.000
	Other at day 1000	1.07	0.525	1.13	0.403

* Results are given as hazard ratios (HR), and p-values for parameter estimates (Cox regression) adjusted for all baseline factors as they appear on the table, as well as by dementia diagnosis. First category of each variable serves as reference (ref).

AD: Alzheimer's dementia. DLB: dementia with Lewy bodies. FTD: frontotemporal dementia. Mixed: mixed Alzheimer's and vascular dementia. MMSE: Mini-mental state examination. Other: other dementia diagnoses. PDD: Parkinson's disease with dementia. Unspecified: unspecified dementia. VaD: vascular dementia.

For DLB, unspecified and other dementias the average HR over the whole observation period is given together with the HR at the beginning of the observation and at day 1 000.

5.3 STUDY III

Detailed results may be found in the corresponding section of article III. Total included patients numbered 11 398, with mean BMI of 24.5 (SD 4.3). Table 2 of article III shows mortality rates per PY in different BMI groups. The lowest weight group presented with the highest mortality rates.

In Cox survival analyses, higher BMI was associated with lower mortality risk. The reference category employed was the 18.5 to 22.9 BMI group. Compared to these individuals, those with BMI under 18.5 presented significantly higher mortality, while all weight categories with BMI above 22.9 had lower risk. The lowest HR of death appeared in the BMI +30 category (HR 0.65; 0.57-0.74 p<0.001). When analyses were stratified by sex, the lowest risk appeared in the obese weight category for men and in the overweight category for women (table 3 of article III).

When BMI splines were introduced into Cox regression analyses, each point increase in BMI was associated with decreased mortality risk up to the end of the overweight category. Results are shown in table 4 of article III. Mortality risk decreased 11% per point increase in BMI in patients with BMI under 22, 5% for patients with BMI 22 to 25 and 3% for patients with BMI 25 to 29.9. Results were not significant in the spline representing the obese patient group. When number of medication was excluded from analyses, each point increase in BMI was associated with higher mortality risk in the obese category (HR 1.04; 95% CI 1.00-1.07).

Spline analyses confirmed the sex differences found in categorical analyses: men presented significant risk reduction with higher BMI in the 18.5 and 25-30 BMI groups. For women, risk decreased with higher BMI only up to the end of the normal category (HR 0.94; 95% CI 0.88 to 1.00 p= 0.05) (table 5; article III). Figure A of article III show plotted results for men and women.

Spline analyses were repeated stratified by age tertile. Only three splines, with

knots at 23 and 30 were used because of the smaller sample sizes. In all age categories, higher BMI was related to lower risk in the lower weight spline (BMI under 23). In the intermediate weight spline (BMI 23-30), a negative association between BMI and mortality risk was demonstrated only in the youngest age group. A trend towards increased risk was observed in the BMI +30 spline in the youngest and oldest age groups. Figure B of article III plots these relationships.

6. DISCUSSION

6.1 STUDY I

In this sample from Karolinska Memory Clinic, SCI patients differed from mild MCI and AD groups. SCI patients were younger, with more years of education, fewer cardiovascular risk factors and higher MMSE scores. They tended to have normal scores in MTA rating of the medial temporal lobe The average CSF measures of dementia biomarkers for this group was within normal parameters: low Aß42 appeared in only 7%, while tau (total or phosphorylated) was high in 12% of the sample. ApoE4 was less prevalent than in the AD group. SCI patients were more likely to recall a family history of dementia and had higher depression scores.

A number of factors might explain these differences. Clinicians had access to CSF and ApoE results during diagnosis, so circularity might have contributed to the results. Traditionally, SCI has been attributed to anxious or depressive symptoms, so the higher prevalence of family history and depressive symptoms among this group might match this conception. Our study does not distinguish between depressive symptoms and a diagnosis of depression, but previous studies suggest that clinically significant symptoms of depression might occur in 8 to 16% of elderly patients.[243] Late-life depression is particularly resistant to treatment and is associated with a wide range of neuropsychological deficits.[244] Processing speed and executive function appear to be particularly affected, which could lead to secondary memory deficits and cognitive complaints.[244] However, in our study SCI subjects only differed in depressive symptoms from AD, and not from MCI. This might suggest that SCI and MCI patients are experiencing depressive symptoms as a reaction to perceived cognitive deficits, displaying insight that disappears in dementia. Furthermore, depressive symptoms might be harder to identify in patients with advanced cognitive decline.

The interplay between depressive symptoms and dementia is exceedingly complex. Depression in mid-life is associated with increased risk of dementia in later years. Depression causes cognitive deficits and although these present a more "subcortical profile" than AD, the differential diagnosis between these conditions may be

difficult. To complicate matters, cognitive deficits in some patients outlast the depressive episode.[244] Low mood, as a symptom, is associated with increased risk of future MCI, particularly of the amnestic type, and seems to interact synergistically with ApoE4.[245] Two recent studies shed some light on the matter.[243, 246] Both are also based on the Karolinska Memory Clinic and should have comparable populations to our study. The first compared CSF profile in depressed elderly subjects with and without AD.[246] This study did not find a relationship between an AD-type profile and depression. On the contrary, a negative relationship was found between depressive symptoms and p- and t-tau in the SCI group and with t-tau in the AD group. Depressed patients were younger in this study than their non-depressed counterparts although they presented similar MMSE.[246] Thus, in this cohort, depression could lead to earlier diagnosis through an increase of executive cognitive symptoms, which are harder to identify with MMSE.[247] This explains the lower age and lower tau values of depressed subjects.

The other study examined temporal lobe atrophy in patients with AD, MCI or SCI, comparing depressed and non-depressed groups.[243] In AD patients, depressive symptoms were associated with less medial temporal lobe atrophy, while patients with SCI and depressive symptoms had smaller hippocampal volumes. This could indicate different mechanisms mediating the association of cognitive and depressive symptoms in the two groups.[243] One possibility is that among AD patients, depression might worsen cognitive symptoms, leading to earlier diagnosis and hence a group with less temporal atrophy. Another possibility would be that depression may require insight that is lost in AD as temporal atrophy progresses. In SCI, depression might be part of the neurodegenerative package, as part of preclinical AD. These two studies raise intriguing questions on the interrelationship between depression and cognition at different stages of the AD-continuum.

The second part of Study I is based on a statistical model created to analyze the likelihood of presenting an AD profile for the participants in the database. Our study included MTA ratings from an experienced observer who was blinded to clinical data. As expected, SCI patients tended to present normal scores. Within the statistical model

higher MTA scores were associated with higher AD-likelihood in the SCI group. The opposite was observed in the MCI group: higher scores were associated with lower AD-likelihood. Since neuroimaging (but not MTA scoring) was available to clinicians during clinical diagnosis, part of these results might be due to circularity: MCI patients with temporal atrophy probably presented clinical characteristics that were atypical for AD since otherwise they would simply have been classified as AD. Since SCI patients are clinically far from dementia, this circularity would have posed less of a problem in the SCI group. A similar finding was observed for central atrophy and confluent WML: within the statistical model, these variables showed a positive association for AD-likelihood in the SCI group and a negative one in the MCI group.

Our study examined a number of variables reflecting cardiovascular risk, such as WML, history of stroke or TIA arterial hypertension, and total number of cardiovascular risk factors. Within the model, the presence of these factors tended to be associated with increased AD-likelihood in the SCI group and decreased AD-likelihood in the MCI group. The interpretation of these findings is not straightforward: as can be observed in table I of the article, there were baseline clinical differences between groups. However, these findings might reflect a fundamental difference in the differential diagnosis posed in SCI and MCI groups. MCIs are demonstrably impaired and the differential diagnosis lies between AD and non-AD – probably vascular – pathology. Although vascular risk factors are associated with AD,[248] they are more tightly linked with vascular causes of cognitive impairment: thus, in this group, vascular risk factors would mark patients who fit less into a pure AD profile. Within the SCI group, the question might be whether patients suffer from a preclinical neurodegenerative process (of any kind) or whether their complaints are functional in nature. Thus, cardiovascular risk factors would make patients more AD-like.

One of the limitations of our study is its cross-sectional design. Only longitudinal follow-up could address questions about progression of atrophy or declining cognition in SCI and MCI subjects. Furthermore, there is some indication that the association between cortical thickness and cognition may be variable: the relationship between cortical

thickness and CSF biomarkers is shaped like an inverted U, with cognitively preserved subjects with transitional CSF profile presenting thicker temporoparietal and precuneus regions.[53] One explanation is that these are individuals with particularly thick cortexes that allow them to remain cognitively intact despite ongoing neurodegeneration, as evidenced by their transitional CSFs. Another possibility is that cortical thickness is dynamic and evolves over the course of the disease, stressing the need for longitudinal studies to evaluate these changing relationships over time.

Patient selection was opportunistic and was based on consecutive memory clinic referrals of subjects with cognitive complaints, irrespective of origin. Thus, ours is a naturalistic sample which reflects the heterogeneity of ordinary clinical practice. Diagnosis followed routine practice and was not constrained by a particular research protocol. This explains why not all tests are available for all patients: some might not have needed, or declined certain procedures. This methodology could make our sample less homogeneous but more representative than selected study populations. Circularity occurs when there is dependency between variables used to define groups at study onset and result variables, and is an obvious problem with this study design. To circumvent this, neuroimaging ratings were evaluated blindly, although clinicians had access to the images while making the diagnosis.

The lack of standardized criteria for SCI is a common problem to all studies dealing with this patient group[31, 61] and hinders comparisons between studies. In keeping with the naturalistic design of our sample, patients were only excluded if they presented with severe comorbidities that made diagnosis uncertain, for example intracranial neoplasms. This explains the high prevalence of parkinsonism in the MCI sample (21%; table I of the article) and hints at these patients possibly presenting cognitive impairment due to Lewy body or subcortical vascular pathology.

A growing number of publications suggest that SCI subjects differ from healthy populations[31, 33, 50, 51, 53, 60, 61, 63, 64, 70, 249, 250] and some SCI subjects may represent the earliest detectable stage of AD.[33, 40, 251] However, identifying subjects who will present

future decline may prove to be difficult. Cognitive complaints with normal neuropsychological testing may be particularly predictive in highly educated subjects where the ceiling effect of testing is a problem.[60] The SCI group in our sample was highly educated, reflecting the composition of urban Sweden in their generation. However, only some of these individuals will develop a neurodegenerative disease and only follow-up can reveal who will progress. The Dubois criteria[252] and National Institute of Aging-Alzheimer's Association (NIA-AA) diagnostic guidelines[9] expand diagnosis of AD into earlier stages. Our study attempts to be part of this effort in isolating factors that might help detect at risk individuals.

6.2 STUDY II

This second study is based on 15 209 patients diagnosed in specialist memory clinics from all over Sweden and included in SveDem between 2008 and 2011. Mortality risk for the different dementia disorders and underlying factors were calculated using HR obtained from Cox hazard regression analyses. Factors such as male gender, higher number of medication, institutionalization, worse cognition (as evaluated by MMSE), higher age and non-AD dementia were associated with higher mortality risk in this study.

In this cohort men presented 56% higher mortality risk than women. This is in accordance with previous studies.[143, 146, 153, 154, 157, 161-164] Some studies have suggested that the influence on gender in mortality risk may be different for different dementia disorders.[142, 150, 158, 166, 167] We found no such association in our sample: when stratified by diagnosis, men presented higher mortality risk in all dementia diagnoses except FTD and DLB, where results were non-significant. The greatest difference between men and women was found for PDD) with 71% higher mortality risk for men.

As expected from previous studies, higher age[143, 150, 153-155] and lower MMSE[157, 169] increased mortality risk. There was a fourfold increase in risk for patients deemed untestable for MMSE, probably revealing a floor effect of testing.

Our study used number of medication as a proxy for comorbidity and found that it was associated with higher mortality risk. Treatment with cholinesterase inhibitors was associated with reduced mortality and cardiovascular events in AD patients in SveDem,[216] so models with and without this variable were run to exclude confounding. In this cohort, cholinesterase-inhibitor treatment was indeed associated with lower mortality but it did not alter other results, and neither did other medication types.

Mortality risk varied by dementia diagnosis: AD presented lower mortality than any other dementia type. Using AD as reference category, the highest crude HR for death was obtained for VaD (HR 2.27, 95% CI 2.08–2.47). This risk remained similar after adjusting for sex, but when adjusting for age and sex PDD became the dementia type with highest risk. As can be seen in table 2 of article II, PDD patients tended to be younger but used more medication than other dementia groups, suggesting that they had more comorbidity, which may explain these results. After additional adjustment for number of medication and when including all the variables in the final model, FTD became the dementia type with highest risk with a twofold increase in risk relative to AD (table 5 of article II). As is evident from table 2 of the article, FTD patients were younger than other groups (average age was 69) and took less medications. Survival in FTD ranges from 3[159] to 9.5[93, 175] years according to previous estimates. FTD had worse survival than AD in most studies,[146] although studies comparing a wide range of dementia types are rare.[146] Even though FTD is a rare condition, it affects relatively young and healthy patients and presents disproportionally high mortality risk, highlighting the need for further research into this condition focusing on causes of mortality.

According to previous literature, AD presents lower mortality than other dementia disorders,[142, 146, 150] although some studies find no difference between conditions[142, 146, 150]. However, few compare a wide range of diagnosis,[142, 146, 150] which makes our study particularly novel. As expected, mixed dementia presented intermediate risk between VaD and AD, possibly due to the higher cardiovascular risk inherent in the "vascular" component. Since cardiovascular causes are the most frequent causes of death across dementia disorders, the gradient of mortality risk from AD – mixed – VaD is

unsurprising.[142, 146, 150] Previous literature shows that AD groups have less comorbidity than other dementia types,[142, 146, 150] and this fits well with the lower number of medication in AD in our cohort (table 2; article II). However, models run with and without controlling for medication did not differ in the relationship in mortality between VaD and AD.

Despite exceptions,[180] most previous studies found worse prognosis for DLB than for AD.[167, 179] In our cohort, DLB had higher mortality risk than AD. When entered as the reference category, DLB had significantly higher mortality risk than AD and mixed dementia, with no differences with PDD or VaD. DLB and PDD share many features with some authors proposing to include both diseases in a common Lewy body dementias (LBD) category,[82] so the similar mortality risk is unsurprising.

The absence of a control cohort with normal cognition is a weakness of this study. SveDem is a quality registry which includes patients diagnosed in regular clinical practice: as such, there is no fixed research protocol for diagnosis and different patients may have followed different diagnostic pathways. The Swedish National Board of Health and Welfare[228] published guidelines on the requirements for a basic dementia diagnostic work-up: in SveDem, over 85% of patients in specialist units fulfill this criteria.[217] In addition, most patients in specialist settings are also examined using an extended work-up according to national guidelines.

The observational nature of this study precludes making inferences on causality. In Study II and III, SveDem had a coverage of over 25% of expected dementia incidence in all Sweden. However, in these two studies only patients from specialist setting were included. Since more than 90% of the specialist units are affiliated to SveDem and the majority of their dementia patients are registered, the coverage is much higher than 25%. Thus, the representativeness of incident dementia cases in Sweden from specialist settings is actually very good. Our study had a follow-up time of 2.5 years which may have been too short to evaluate changing mortality risks over time if mortality in a particular dementia group concentrates at one or another stage of the disease. Longer

follow-up times in SveDem will be able to answer this question in the future.

Length bias occurs when studies include prevalent cases and patients with rapidly progressive disease die before recruitment.[143] The inclusion of only incident cases is a strength of this study, and should help control this bias. The selection of specialist memory clinics was meant to improve diagnostic reliability but could be a problem if memory clinic and primary care patients differ significantly. Indeed, previous studies on SveDem suggest that primary care patients are older and have more comorbidity and that the diagnostic process is different.[214, 227] In order to determine whether the exclusion of primary care had led to bias, analyses were repeated with all patients (specialist and memory clinics) included in SveDem between 2007 and 2012. As was shown in table 14, this did not substantially alter our results.

The wide range of diagnoses examined and the large number of patients are the main strengths of our study. This study is the largest prospective study of its kind to examine mortality in incident dementia.

6.3 STUDY III

Article III explores the relationship between mortality and BMI at the time of dementia diagnosis. The cohort includes 11 398 patients diagnosed in memory clinics between 2008 and 2011 and for whom complete data on BMI was available.

Previous studies have analyzed mortality and BMI in different age groups but this is the first large study to evaluate this relationship in a population with newly-diagnosed dementia. Low BMI was associated with higher mortality risk after adjusting for sex, age, MMSE, dementia diagnosis and number of medication. The obese weight group presented the lowest mortality risk, although a significant difference was not demonstrated between the obese and overweight groups. When analyzed as splines, each point increase in BMI up to BMI 29.9 resulted in a significant decrease in mortality risk, with the mortality curve flattening out after BMI 30 (figure 1; article III). Data from

SveDem has previously shown that more than a quarter of the patients at diagnosis have BMI under 22 and underscore the importance of nutritional evaluation for dementia patients.[253]

There were sex differences in the relationship between mortality risk and BMI: the lowest risk occurred in the overweight group in women and in the obese weight group for men. Furthermore, spline analyses showed that risk flattened out at lower BMIs for women than for men, implying that men benefited from higher BMIs (figure 1a; article III).

The composition of our sample included few patients with BMI over 35 and precludes conclusions in this patient group. Furthermore, spline analyses repeated without adjusting for medication showed increased risk after BMI 30, suggesting that after this point, comorbidity (reflected in the number of medication) may be playing a part in increased risk.

A review of literature reveals a complex association between BMI and mortality in special populations. The BMI associated to minimum mortality increases with age[189, 254, 255] and occurs in the overweight or obese weight group for older populations,[190, 191, 255, 256] although some have described increases in mortality in the obese old.[191, 257, 258] A previous study found 17% lower mortality risk in obese adults over 75 compared to their normal-weight peers.[189] In our study, the reduction in risk was 27% and 32% in the overweight and obese groups respectively (table 3; article III).

The optimal BMI for minimum mortality risk could be higher in men than in women[190, 255] although some studies find different associations.[191] In one study, the lowest mortality appeared with BMI between 18.5 to 25 in women over 55, but between 25 and 30 for men.[255] This agrees with our present findings. The reasons behind this connection may be biological or social,[190, 259, 260] and require further investigation.

This finding of lower mortality in the presence of a traditional cardiovascular risk

factor is termed "reverse epidemiology" and has been described in chronically or acutely ill populations such as renal failure, stroke, cardiac insufficiency, malignancies and acquired immunodeficiency syndrome (AIDS).[203-205] The same concept applied to obesity is termed the "obesity paradox" and has also been described among the elderly.[190, 200, 201] The novelty of our study resides in describing this phenomenon among a new population; that of patients with dementia, but the concept itself has been known since the early 00´s[261]. Although this effect has been evident in repeat observations, the causes behind it remain controversial.[195] The explanations for this phenomenon are varied, ranging from bias to the presence of competing hazards or different biological mechanisms such as catabolic states or inflammation.[194, 195, 206, 262] Indeed, this article motivated a letter to the editor by Moga et al[262] in which issues of reverse causation and bias were raised. This allowed us to respond with a letter of our own, which we hope contributes to this fascinating subject. Moga et al had concerns about selection bias, since our original article included only specialist clinic patients. Indeed, primary care patients in SveDem present lower mortality risk (HR of 0.45; 95% CI 0.42-0.49) so these concerns are founded.[263] In table I of the response letter,[263] we show analyses on the whole database and primary care. Results were often not significant in primary care and less reliable due to missing BMI data: however, the obese group still presented significantly lower mortality than the reference category in primary care.[262]

Missing data on BMI was a concern and hard to correct given the structure of SveDem. However, the category of missing BMI presented similar mortality risk than the group with BMI between 25-29.9. In order to remove the effects of persons at the extremes of the scale, spline analyses were repeated only for subjects with BMI 20 to 31. Results are shown in table II of the response letter[263]: higher BMI is still associated with reduced mortality risk even under these conditions.

Another possible weakness of this study is the use of BMI as a nutritional measure[255] and the lack of follow-up for BMI. However, as was argued in the introduction to this thesis, BMI is widely available and predicts cardiovascular health and mortality reasonably well. Changes in BMI, rather than a single measure might be

more sensitive to prognosis.[196, 210] In one study, patients over 70 who either lost or gained weight presented higher mortality risk than their stable-weight counterparts.[254] SveDem is designed with annual follow-ups and hitherto about 50% of the SveDempatients are followed up at least once[219] while three and four year follow-ups comprise small sample sizes. However, the follow-up of BMI data in SveDem over time is one of the obvious future studies to do.

Other issues presented by Moga et al[262] have to do with the causal chain of events between dementia and low BMI: dementia is known to cause weight loss, which can precede diagnosis. Patients with dementia often forget to eat and have swallowing difficulties, and patients with weight loss display worse prognosis.[264] The descriptive nature of SveDem precludes making inferences on causality but previous studies show that interventions that cause weight gain in advanced dementia are associated with reduced mortality.[210] Our current methods do not allow the determination of the mechanisms that link lower BMI to higher mortality risk in dementia, but independent of its causal mechanism, this observation is valuable. For a clinician facing a patient with dementia the causal relationship may well be irrelevant. Rather, this study underlines the need for complete nutritional assessments of patients with dementia and proves the utility of BMI for prognosis.

In the future, longitudinal prospective studies with cognitively-intact controls could determine if patients with dementia benefit from higher BMIs than healthy older adults. Interventional studies would be needed to determine the treatment strategies to apply to this group. At present, low BMI identifies dementia patients at higher risk of death.

7. CONCLUSIONS

1. In the Karolinska Memory Clinic, subjective cognitive impairment (SCI) patients are a distinct group: younger than mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients, with more years of education, lower frequency of cardiovascular risk factors, higher Mini-Mental State Examination (MMSE) scores and normal dementia biomarkers in the cerebrospinal fluid and normal medial temporal atrophy ratings. Generalized central and cortical atrophy and confluent white matter lesions were less frequent, as was apolipoprotein E4. SCI patients presented more symptoms of depression as evaluated by the Cornell scale of depression in dementia than the AD group, but did not differ from the MCI group.
2. The logistic regression model containing age, sex, MMSE Aβ42/t-tau (amyloid-beta 42 / total tau) quotient and p-tau (phosphorylated tau) accurately classified 94.9% of the sample. Within this model, factors directly or indirectly representing cardiovascular risk tended to increase the AD-likelihood in the SCI group but decrease it in the MCI group, possibly speaking for a fundamental difference in the differential diagnosis that is posed in these two conditions.
3. Once dementia is diagnosed, the dementia type and other baseline factors can predict mortality risk. Male gender, higher age, lower MMSE, higher number of medication, institutionalization, and non-AD dementia are associated with worse prognosis. In crude analyses vascular dementia (VaD) presented the highest mortality risk, while in age, gender and medication adjusted analyses frontotemporal dementia (FTD) became the dementia with highest risk. This suggests that FTD is particularly deadly, considering that it affects younger and healthier individuals.
4. Low body mass index (BMI) is associated with increased mortality risk. The BMI range associated with minimum mortality is sex dependent. Higher BMI is associated with lower mortality risk up to BMI 24.9 kg/m^2 in women and up to 29.9kg/m^2 in men. Our findings underscore the clinical importance of nutritional assessment for patients diagnosed with dementia.

8. VERSIÓN REDUCIDA EN CASTELLANO

8.1 INTRODUCCIÓN

8.1.1 Evolución del concepto y definición de demencia

La demencia ha acompañado a la humanidad desde el principio de los tiempos, y ha sido reconocida como enfermedad desde épocas antiguas.[1, 2] Areteo de Capadocia pudo ser el primero en distinguir entre el *delirium* como un cuadro reversible y la demencia, que él describió como un cuadro permanente y progresivo.[2] Tanto Hipócrates como Galeno fueron conscientes de que estas enfermedades podían tener su origen en procesos primarios cerebrales o ser secundarios a enfermedades que afectaran a otros órganos.[2] Tal vez fuera Cícero el primero en distinguir la demencia del envejecimiento normal y en proponer la actividad intelectual como un modo de prevenir el deterioro cognitivo.[3]

La descripción original de Alois Alzheimer de la enfermedad que lleva su nombre no despertó mucho interés en un primer momento, tal vez porque el propio Alzheimer estaba convencido de que era una enfermedad bastante infrecuente. En la base de datos Pubmed® sólo constan 47 publicaciones con el término "Alzheimer" entre 1963 y 1973. Por orden del Congreso de Estados Unidos, en 1974 se creó el *National Institute of Aging* (NIA, Instituto Nacional de Envejecimiento), y a partir de ahí se produjo un cambio.[2, 4] En 1974 se publicaron 14 artículos sobre enfermedad de Alzheimer (EA), 43 en 1975 y 110 in 1980. Desde entonces la progresión fue exponencial, llegando a alcanzar un total de 4 988 publicaciones indexadas en 2012. Otras enfermedades como la demencia de cuerpos de Lewy (DLB) o la demencia frontotemporal (DFT) se han sumado al panorama de modo que en la actualidad la demencia se comprende como un conjunto de síndromes causados por una variedad de enfermedades y alteraciones anatomopatológicas.

La Organización Mundial de la Salud (OMS)[5] define la demencia como un síndrome causado por una enfermedad cerebral, generalmente crónica y progresiva, en la que se alteran múltiples funciones corticales, con un nivel de conciencia preservado. Para el diagnóstico de demencia se debe demostrar además un deterioro desde niveles

superiores de funcionamiento previos y se debe excluir que el deterioro ocurra en contexto de un *delirium* o de trastornos psiquiátricos mayores. El grupo de trabajo del *National Institute for Aging-Alzheimer's Association* (NIA-AA, Instituto nacional estadounidense para el envejecimiento – Asociación de Alzheimer) estipula que este deterioro cognitivo debe quedar corroborado mediante una combinación de la historia clínica y el examen neuropsicológico. Además, para hacer el diagnóstico de demencia el déficit cognitivo debe afectar al menos a dos dominios: memoria, razonamiento, capacidad visuoespacial, lenguaje, o personalidad y comportamiento.[6] Aunque este síndrome afecte principalmente a personas mayores, el deterioro sobrepasa lo esperado con el envejecimiento normal.

Existen varias clasificaciones de las demencias, entre ellas la de la Clasificación Internacional de Enfermedades (CIE-10)[5] y la del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-IV y DSM-5), además de guías clínicas para tipos particulares de demencia.[5, 6, 9-13] Sin embargo, existe un solapamiento entre las distintas enfermedades y entre las fases preclínicas (o pre-demencia) y la fase de demencia.[9] Estas áreas de incertidumbre son consecuencia de las limitaciones naturales de todos los sistemas de clasificación y de la variedad biológica en la presentación de las enfermedades.

8.1.2 La enfermedad de Alzheimer

8.1.2.1 Primera descripción y concepto actual de la enfermedad

En 1906 Alois Alzheimer describió el caso de "Auguste D", una mujer de 51 años que presentó un cuadro de demencia y en cuya autopsia descubrió placas amiloides y ovillos neurofibrilares. En 1911 Alzheimer publicó un segundo caso, el de un varón de 56 años que sólo presentó lesiones anatomopatológicas en forma de placas. Las secciones histológicas se han conservado hasta nuestros días, permitiendo confirmar los hallazgos de Alzheimer y excluir mutaciones de la proteína precursora de amiloide (PPA) en estos pacientes.[14, 15] Alzheimer no estaba seguro de la naturaleza de esta enfermedad, aunque

pensó que podría tratarse de una presentación temprana de demencia senil o bien de otra entidad diferente. No obstante, Emil Kraepelin, que era supervisor de Alzheimer y el psiquiatra de más renombre a nivel mundial de su tiempo, la incluyó con el nombre de enfermedad de Alzheimer (EA) en su tratado de Psiquiatría de 1910[3]. Otros patólogos dieron validez a estas descripciones histológicas, pero la EA siguió considerándose como una enfermedad que solo afectaba a personas jóvenes hasta varias décadas después.

Hoy en día, se entiende la EA como una enfermedad compleja en la que la enfermedad neuropatológica ("EA patológica", EA-P) debe distinguirse de su manifestación clínica ("EA clínica", EA-C).[16, 17] Existen dos grupos de criterios para investigación en EA y ambos emplean biomarcadores.[18] El *International Working Group* (IWG) propone criterios para "EA preclínica" y "EA presintomática". En este último grupo se incluyen sujetos asintomáticos con mutaciones autosómicas dominantes para EA hereditaria. Los individuos sintomáticos se clasifican en "EA" con subgrupos: "EA prodrómica" (deterioro cognitivo leve, DCL) y "demencia tipo Alzheimer". El otro grupo de criterios los publicó la NIA-AA. Cuando hay disponibilidad de biomarcadores, los individuos se clasifican en un estadio asintomático llamado "EA preclínica", un estadio de DCL causado por EA y un estadio de demencia, "demencia causada por EA". Cuando no existen biomarcadores, la clasificación se basa en criterios clínicos para definir la "EA posible o probable" y el "DCL". La tabla 3 de la versión en inglés de esta tesis compara ambas clasificaciones.

8.1.2.2 Enfermedad de Alzheimer patológica (EA-P)

Los cambios anatomopatológicos en la EA consisten en la acumulación de placas seniles de β amiloide (βA) y ovillos neurofibrilares (*neurofibrillary tangles*, NFT) en grados variables de intensidad y distribución.[19] Los NFT son depósitos intraneuronales compuestos principalmente por proteína tau patológica, que pueden visualizarse con tinciones histoquímicas o inmunohistoquímicas dirigidas contra epítopos de tau o tau fosforilada. En estadios tempranos su extensión puede limitarse a áreas límbicas, pero a medida que avanza la enfermedad se extienden a otras áreas cerebrales, incluyendo la

corteza cerebral, núcleos subcorticales y algunas áreas troncoencefálicas.[20] La secuencia comienza en el córtex entorrinal, extendiéndose al hipocampo y neocórtex, aunque existen excepciones. [20, 21] Las placas seniles son depósitos extracelulares de péptidos βA. Cuando se sitúan en el centro de un racimo de neuritas distróficas – que suelen tener inmunorreactividad positiva para tau fosforilada – se llaman placas neuríticas. Las placas no neuríticas pueden presentarse como placas difusas, "placas de lana y algodón", lagos de amiloide y bandas subpiales.[20] Las placas de amiloide son heterogéneas y actualmente se cree que son las placas neuríticas las que tienen mayor potencial para ocasionar daño neuronal.[20] El depósito de βA en el cerebro sigue una secuencia concreta, comenzando en el neocórtex (fase de Thal 1), seguido de regiones alocorticales (fase 2 de Thal), núcleos diencefálicos, estriado, núcleos colinérgicos y prosencéfalo basal (fase 3 de Thal), otros núcleos troncoencefálicos (fase 4 de Thal) y cerebelo (fase 5 de Thal).[22] Las lesiones de EA pueden presentarse en individuos sin deterioro cognitivo y preceden, en años, el inicio de los síntomas. En sujetos con síntomas, niveles intermedios o altos de patología EA se consideran suficientes para explicar los problemas cognitivos y confirmar un diagnóstico de EA.[17, 19]

Los criterios de Braak y Braak[27] todavía están en efecto para NFT, aunque la NIA-AA prefiere las fases de Thal para describir placas de amiloide,[18, 20] mientras que criterios del CERAD (*Consortium to Establish a Registry for Alzheimer's Disease*) se emplean para estadificación de placas neuríticas.[28] Así, la NIA-AA recomienda una escala "ABC" (Amiloide, Braak, CERAD) para la clasificación de cambios patológicos de EA (tabla 4). La NIA-AA también recomienda que se registren la patología vascular y los cuerpos de Lewy (*Lewy bodies*, LB), así como la esclerosis hipocampal y las inclusiones de TDP-43 (*transactive response DNA-binding protein 43 kDa*).[19, 20, 22]

8.1.2.3 Enfermedad de Alzheimer clínica (EA-C)

El cuadro típico de la EA se caracteriza por un comienzo de deterioro cognitivo insidioso y progresivo de suficiente gravedad como para cumplir criterios de demencia, y por la afectación de dos o más áreas cognitivas (tablas 5 y 6). La presentación amnésica

es la más típica, con déficits en memoria episódica. Las presentaciones no amnésicas incluyen cuadros con alteraciones del lenguaje como la anomia, de las capacidades visoespaciales o de las funciones ejecutivas. Además, para el diagnóstico de EA no debe haber evidencias de daño vascular cerebral extenso ni en la historia clínica ni en las pruebas de neuroimagen.[6] La conciencia de enfermedad puede o no estar preservada y es frecuente la asociación de síntomas depresivos. Las habilidades sociales y las actividades básicas de la vida diaria tienden a preservarse hasta estadios avanzados de la enfermedad.[29]

Existen dos presentaciones no amnésicas que merecen especial atención. Una, es la atrofia cortical posterior.[6] En este síndrome coexisten elementos del síndrome de Balint, tales como dificultad para integrar la percepción de todo el campo visual, para dirigir la mirada o para alcanzar objetos presentados visualmente, con apraxia, síndrome de Gerstmann y otros síntomas más típicos de EA.[29] Otra es la afasia logopénica primaria progresiva. En este síndrome, el déficit más evidente aparece en la búsqueda de palabras, aunque deben coexistir déficits en al menos otro dominio cognitivo para cumplir criterios de EA según la NIA-AA (tabla 6).[6] La afasia primaria progresiva también puede asociarse a demencia frontotemporal (DFT), especialmente en casos con presentación agramatical. Sin embargo, aunque el subtipo de afasia primaria progresiva pueda ayudar a predecir si subyace EA o DFT, ningún criterio clínico es capaz de predecir el diagnóstico en todos los casos.[30]

8.1.2.4 Estadios preclínicos y predemencia de la enfermedad de Alzheimer

El término "quejas cognitivas subjetivas" (QCS) se aplica a un grupo heterogéneo de pacientes que presentan quejas cognitivas sin evidencia objetiva de deterioro en el estudio neuropsicológico.[31] La neurodegeneración probablemente comience décadas antes del inicio de los síntomas,[32, 33] y se calcula que el estadio de deterioro cognitivo leve (DCL) dura 7 a 10 años.[34] Así, es natural buscar los estadios más tempranos de esta enfermedad entre pacientes que presenten síntomas cognitivos sin evidencia demostrable de deterioro.[9, 35] Las QCS afecta a un alto porcentaje de los pacientes que acuden a

clínicas de memoria a nivel mundial[36, 37] y, por lo tanto, representa un problema clínico relevante. El concepto ha evolucionado desde que Reisberg definió el estadio 2 de la escala *Global Deterioration Scale* (GDS),[39] que es equivalente a QCS, y en la actualidad son muchos los autores que apoyan la existencia de este síndrome como un estadio temprano de enfermedad neurodegenerativa, en particular de la EA.[40, 41] Este concepto puede ser especialmente válido cuando hay acceso a biomarcadores y estos son sugerentes de EA.[9] En otros casos, el diagnóstico es más controvertido.

Hoy en día la EA es un diagnóstico establecido, aunque persisten áreas de incertidumbre. El DCL es más heterogéneo y existen dudas en cuanto al pronóstico de muchos pacientes. Todos estos problemas se acrecientan en los pacientes con QCS, por definición un diagnóstico sin variables "duras" y en el que la investigación se ha centrado sobre todo en aspectos de depresión y personalidad de los pacientes.[31] La diversidad de los pacientes con QCS y de los métodos de estudio contribuye a esta confusión: mientras que algunos trabajos se centran en la población general,[42-51] otros reclutan pacientes desde unidades de memoria.[52-54] La tabla 7 resume los estudios sobre prevalencia de QCS.

Pese a estos problemas, existen evidencias para considerar las QCS como el estadio más temprano de un continuo QCS-DCL-EA. Los resultados de algunos estudios parecen indicar que los sujetos con QCS tienen un riesgo aumentado de deterioro cognitivo en el futuro,[51, 59-61] aunque no todos los autores encuentran esta asociación.[62] Como puede verse en la tabla 8, las QCS se asocian a una razón de probabilidades (*odds ratio*, OR) para deterioro cognitivo posterior entre 1,5 a 8,5 en comparación con los controles. La presencia de determinados factores, como las lesiones de sustancia blanca cerebral o el alto nivel educativo, aumentan la fuerza de esta asociación.[59, 60] Es posible que los individuos con mayor nivel educativo sean más sensibles para su propio deterioro que los tests neuropsicológicos, o que el efecto techo de estos tests sea particularmente relevante en este grupo. Además, los individuos con alto nivel académico suelen tener ocupaciones con mayores requerimientos cognitivos, que podrían poner de manifiesto la existencia de déficits más sutiles.

Los sujetos con QCS también difieren de la población general en las pruebas de neuroimagen.[63, 64] Se ha demostrado que los pacientes con QCS tienen menor volumen del hipocampo que los controles,[64] así como una reducción del volumen de regiones temporomediales y frontotemporales,[63] con una distribución similar a la que se ha encontrado en pacientes con DCL. La neuroimagen funcional demuestra aumento de activación para ciertas tareas cognitivas en la EA, el DCL y en sujetos portadores del alelo ε4 de la apolipoproteina ε (APO ε4),[65, 66] indicando la presencia de reclutamiento compensatorio. La intensidad de esta hiperactivación se ha correlacionado con el deterioro cognitivo subsiguiente del paciente.[65] Este patrón se ha reproducido en el estado de QCS, con un aumento de activación en la corteza prefrontal dorsolateral y premotora izquierda,[67] el tálamo, el cíngulo posterior, ambos caudados, el hipocampo izquierdo y la región parahipocampal[68] en distintas tareas. Además, mediante tomografía de emisión de positrones con fluorodesoxiglucosa (FDG-PET) se ha demostrado reducción del metabolismo en regiones parahipocampales, parietotemporales, frontales inferiores, giro fusiforme y tálamo, replicando los hallazgos de sujetos sanos con alto riesgo de EA (formas familiares autosómico-dominantes de EA, familias con altas prevalencias de EA u homocigotos APO ε4) y de pacientes con DCL.[33]

Las QCS se asocian a lesiones de EA en la autopsia,[69, 70] y marcadores de EA en el líquido cefalorraquídeo (LCR)[71]. La teoría actual sobre la evolución de los marcadores de EA propone una caída precoz del βA seguida de un aumento de tau en estadios posteriores.[54] Si el estado QCS es parte de la historia natural de la EA, los biomarcadores deberían corresponderse con las fases más tempranas de esta evolución. Esto encaja con la correlación demostrada entre los niveles de βA de 42 aminoácidos (βA42) y el rendimiento en tareas semánticas y de memoria de trabajo en individuos con QCS y controles, mientras que los niveles de tau predicen mejor la cognición de los pacientes con DCL.[72]

Los sujetos con QCS y los controles también difieren en marcadores de atrofia y depósito amiloide visualizados con tomografía de emisión de positrones (PET) con compuesto B de Pittsburgh (PiB-PET).[73] En algunos trabajos los sujetos sanos con

depósito alto de PiB tenían lóbulos temporales de mayor tamaño que los sujetos sanos con depósito de PiB bajo.[74] Esto sugiere que sólo los sujetos que constitutivamente tengan lóbulos temporales de gran tamaño pueden mantenerse asintomáticos con altas cargas de amiloide, o bien que el amiloide en sí mismo aumenta el volumen de los lóbulos temporales en fases tempranas. La relación entre volumen cortical y amiloide parece describir una curva en U.[53] Sin embargo estos estudios son transversales y se necesitan estudios longitudinales para determinar si sus hallazgos corresponden a grupos de pacientes distintos o a pacientes en distintas fases de la misma enfermedad.

El DCL describe un estadio de deterioro cognitivo apreciable en el cual aún se conserva la independencia funcional.[75] Cuando la causa es la EA, el DCL se considera un estadio predemencia en el curso de la EA. La NIA-AA requiere la existencia de una caída respecto al nivel de funcionamiento previo, que el deterioro sea demostrable en una o más áreas cognitivas, y que el paciente mantenga su independencia para las actividades de la vida diaria. Si aparece una afectación social u ocupacional se considera que el paciente ya tiene una demencia y el término DCL deja de ser aplicable.

8.1.2.5 Instumentos diagnósticos: el papel de los biomarcadores

Los biomarcadores se definen como parámetros anatómicos, fisiológicos o bioquímicos que se detectan "in vivo" y que reflejan aspectos específicos de la fisiopatología de una enfermedad particular. En los criterios de 2011, la NIA-AA clasificó los biomarcadores de EA en dos categorías basándose en su especificidad.[17] Así, una categoría incluye los biomarcadores de acumulación de βA, tales como demostración de amiloide en PET o el descenso de βA42 en LCR. Otra categoría incluye biomarcadores de degeneración o daño neuronal, tales como tau alta en LCR, descenso de captación de FDG en PET en corteza temporoparietal o atrofia en áreas típicas de EA en pruebas de neuroimagen estructural.[9, 76] Los biomarcadores que reflejan patología amiloide aparecen entre 10 y 20 años antes de los primeros síntomas. Los biomarcadores de daño neuronal y alteración funcional llegan más tarde, en paralelo con el empeoramiento cognitivo.[17]

Siguiendo los criterios de la NIA-AA, los biomarcadores se emplean en fases preclínicas para establecer la presencia de EA-P en sujetos de investigación asintomáticos o sutilmente sintomáticos. En las fases DCL y DTA los biomarcadores son complementarios al diagnóstico clínico, que puede hacerse exclusivamente con criterios clínicos si no se dispone de biomarcadores.[17, 75] En el DCL, de acuerdo con la NIA-AA, los biomarcadores son una herramienta de investigación y no forman parte de la rutina clínica.[75]

8.1.3 Demencia vascular

La demencia vascular (DV) se define como una pérdida de capacidad cognitiva con repercusión en las actividades de la vida diaria resultante de enfermedad cerebrovascular isquémica o hemorrágica, o de alteraciones cardiovasculares o circulatorias que afectan a la función cerebral.[77] Las causas vasculares se suponían las principales responsables del deterioro cognitivo hasta los años 70 y 80, cuando el enfoque se desvió hacia causas neurodegenerativas de demencia.[78] En la actualidad, existe un renovado interés en la patología vascular y en su interacción con la EA.[79]

La DV se considera la segunda causa de demencia, después de la EA,[77, 80] aunque las estimaciones de prevalencia varían dependiendo de la definición empleada.[78] A diferencia de lo que ocurre en la EA, la DV es más frecuente en varones[77] y los déficits mnésicos no son la alteración principal.[78] El cuadro clínico puede ser variado, desde demencias post-infarto al estado lacunar o enfermedad de Biswanger.[77] La clínica depende de las regiones cerebrales afectadas y varían desde afasia o apraxia como síntomas más propios de afectación cortical, hasta síntomas disejecutivos y trastornos de la marcha como marca de patología subcortical.[79] La evolución de los síntomas es variable, con curso agudo o subagudo que puede mejorar, estabilizarse o progresar de forma gradual o escalonada.[79]

8.1.4 Demencia mixta: entre la demencia tipo Alzheimer y demencia vascular

En realidad no existe un límite claro entre la EA y la DV. Los factores de riesgo vascular, entre ellos la hipertensión arterial y la resistencia a la insulina, se han relacionado tanto con la EA como con la DV.[78] El alelo APOE ε4 aumenta el riesgo de EA pero también de infartos cerebrales,[81] y la mayoría de los pacientes de edad avanzada que presentan EA también tienen algún grado de patología vascular[77, 81] que podría potenciar el efecto de la patología tipo Alzheimer. [77] No está claro si ambos procesos tienen un efecto aditivo o sinérgico en la progresión hacia la demencia.[78] En el estudio de las órdenes religiosas Rush, los infartos macroscópicos aumentaban el riesgo de demencia de una forma independiente y no sinergística.[81] Este solapamiento entre entidades podría indicar que algunos factores de riesgo de la EA actuarían a través de mecanismos vasculares, y no sobre la patología amiloide.[81]

Una proporción importante de pacientes presenta características tanto de EA como de DV. El término demencia mixta se aplica a este grupo, que expresa grados variables de afectación de funciones mnésicas o ejecutivas, o de otras áreas cognitivas, unida a evidencia de enfermedad cerebrovascular.

8.1.5 Demencias causadas por cuerpos de Lewy: demencia con cuerpos de Lewy y enfermedad de Parkinson con demencia

Aunque inicialmente se describieran por separado, en la actualidad se acepta que la demencia con cuerpos de Lewy (*Dementia with Lewy Bodies*, DLB) y la enfermedad de Parkinson con demencia (EPD) comparten un sustrato fisiopatológico común y que pueden considerase como dos entidades dentro de un mismo *continuum*.[82] Se ha propuesto el término de "demencias con cuerpos de Lewy" para englobar ambas entidades. En estas enfermedades aparecen inclusiones intraneurales de alfa-sinucleína formando cuerpos de Lewy (*Lewy bodies*, LB) y neuritas de Lewy, con pérdida neuronal, a menudo acompañadas de algún grado de patología de EA. La prevalencia de esta

entidad se estima en torno al 25% de los pacientes con enfermedad de Parkinson (EP), y aumenta con la duración de la enfermedad. Existe menos información sobre la prevalencia de DLB, que probablemente se encuentre subestimada.[83] Se ha calculado que la DLB podría representar entre el 0 y el 24% de las demencias.[84]

8.1.5.1 Demencia con cuerpos de Lewy

En la DLB los aspectos patológicos arriba descritos se acompañan de un síndrome clínico caracterizado por un cuadro de deterioro cognitivo de rápida progresión dominado por dificultades en la capacidad de atención, la solución de problemas y las capacidades visoespaciales y unido a fluctuaciones en el funcionamiento cognitivo, alucinaciones visuales, parkinsonismo e hipersensibilidad al tratamiento con neurolépticos.[86] Los pacientes con DLB también pueden presentar trastorno de conducta en sueño REM, disautonomía, delirios y alucinaciones en otras modalidades. En la actualidad, se acepta que el 60% de los casos de EA confirmados patológicamente pueden presentar grados variables de patología con LB.[85] Por este motivo, los nuevos criterios diagnósticos no sólo consideran el cuadro clínico, la intensidad y la extensión de la patología con LB, sino también las lesiones de EA.[13] Tanto en la EP como en la DLB se demuestra hipocaptación del transportador activo de dopamina (DAT, *dopamine active transporter*) en el estriado en la neuroimagen funcional, y este hallazgo puede ayudar a distinguir ambas entidades de la EA. La hipoperfusión o hipometabolismo occipital sin atrofia es otra marca distintiva (tabla 9).[13, 85]

8.1.5.2 Enfermedad de Parkinson con demencia

El cuadro de demencia asociado a la EP normalmente se inicia unos 10 años o más después de los primeros síntomas motores. Desde el punto de vista anatomopatológico y neuroquímico, la EP se caracteriza por la presencia de neuritas y LB en la sustancia negra y la pérdida de dopamina en el tracto nigroestriatal.[87] El síndrome cognitivo es muy similar al de la DLB.[85] Sin embargo, ambas entidades difieren en la edad al inicio de los síntomas, la secuencia de aparición de síntomas motores y cognitivos

y la respuesta a la levodopa. Para diferenciar ambas entidades, se ha establecido arbitrariamente el punto de corte de un año entre el comienzo de los síntomas motores y el de los síntomas cognitivos (tabla 9).[10] Así, si el parkinsonismo precede a los déficits cognitivos en un año, o más, el paciente recibe el diagnóstico de EPD.[85]

8.1.6 Degeneración lobular frontotemporal

La degeneración lobular frontotemporal (DLFT) es una causa frecuente de demencia presenil. Se puede presentar como diversos síndromes clínicos, que incluyen trastornos motores o del lenguaje y alteraciones de conducta. La patología subyacente es impredecible y heterogénea, pero lo más característico es la pérdida de neuronas asociada a gliosis y espongiosis de distribución frontotemporal.[91, 92] Pueden aparecer inclusiones positivas para tau con predominio de tres o cuatro repeticiones (3R y/o 4R), o inclusiones negativas para tau y positivas para ubiquitina.[92] Cerca del 40% de los pacientes tienen historia familiar de la enfermedad, pero sólo en algunas familias se han identificado causas genéticas.[91]

La forma más frecuente de la demencia frontotemporal es la variante conductual (vcDFT). Esta forma de DLFT se caracteriza por un deterioro progresivo de la personalidad, el comportamiento social y la cognición y se relaciona con una degeneración de las regiones anteriores de los lóbulos frontales y temporales.[89, 90] La tabla 10 resume los criterios internacionales publicados en 2011.[89] Estos criterios tienen una sensibilidad alta (86%) para vcDFT[89], aunque la naturaleza insidiosa de la enfermedad junto con la proliferación de síntomas psiquiátricos lleva con frecuencia a errores diagnósticos.[90] La progresión es rápida y los pacientes fallecen unos 5,4 años después del diagnóstico, en promedio,[93] con menor supervivencia si existe una enfermedad de motoneurona asociada.[94] La excepción a este mal pronóstico son los casos de "fenocopia", que no muestran alteraciones en neuroimagen ni deterioro progresivo.[93]

Otra forma de presentación es la afasia primaria progresiva, en la que el déficit de lenguaje domina el cuadro. La afasia primaria progresiva puede tener otras causas, entre

ellas la EA, pero tanto la variante no fluente como la variante semántica se asocian a DLFT en el 70% de los casos.[90]

8.1.7 Índice de masa corporal

A lo largo del tiempo se han propuesto diversas medidas de peso corporal y adiposidad como marcadores del estado nutricional y del riesgo cardiovascular.[95, 96] Galileo Galilei fue el primero en describir la ley cuadrático-cúbica[97], que establece que cuando una forma crece en tamaño, su volumen aumenta en mayor medida que su superficie. De hecho, el nuevo volumen es proporcional al cubo del multiplicador, y la nueva superficie es proporcional al cuadrado del mismo.[98] Esto tiene implicaciones importantes en todas las áreas de la ciencia, y explica por qué los animales de mayor tamaño tienen huesos más gruesos de lo que se esperaría simplemente al aumentar el tamaño de sus parientes de menor envergadura.[99] Siguiendo esta ley, y si la forma del cuerpo no cambiase, al modificarse el tamaño el peso sería proporcional a la estatura elevada a la tercera potencia, tal como se representa en el índice de Rohrer (W/H3, donde W=peso y H=altura).[96] El índice ponderal de Livi aplicó este concepto a poblaciones pediátricas, y se calcula como la raíz cúbica del peso dividida por la estatura.[96] Las *ratios* cúbicas entre peso y estatura son válidas para organismos con escalas isométricas, en las que las proporciones del cuerpo no varían al cambiar de tamaño. Sin embargo, los mamíferos presentan proporciones alométricas: las proporciones cambian a lo largo del desarrollo del individuo, y entre individuos de distintos tamaños.[101]

Quételet comprendió estos problemas en 1842.[102] Observó que la ley cuadrático-cúbica se mantiene sólo en el primer año de vida y que el incremento ulterior de peso en la infancia es menor al esperado. Comprobó que un exponente de 3 representa el crecimiento de los recién nacidos y lactantes, un exponente de 2 el de los niños, y un exponente de 2,5 el de los adultos. Sin embargo, finalmente propuso una *ratio* homogénea con el peso en el numerador y la estatura al cuadrado en el denominador, que se ha convertido en el índice peso-estatura de mayor difusión.

$$Índice\ de\ masa\ corporal\ (IMC) = \frac{peso\ (kg)}{[estatura\ (m)]^2}$$

En 1972, Keys et al[96] sugirieron que esta era la fórmula que mejor se correlacionaba con medidas de pliegue adiposo y densidad corporal, y la llamaron índice de masa corporal (IMC). Desde entonces, el IMC se ha convertido en una medida básica para evaluar el estatus nutricional,[103, 185] y para emitir recomendaciones de salud.[95] Es fácil de obtener y fácilmente reproducible.[95] Además su asociación con la morbilidad de la población, especialmente la morbilidad cardiovascular, es bien conocida desde los años 70.[104, 105] La OMS usa el IMC para clasificar a los adultos en bajo peso, peso normal y obesidad. Los puntos de corte para estas categorías se pueden ver en la tabla 11.

En realidad el IMC no aporta información sobre la composición del cuerpo. Esta limitación es de particular trascendencia en los atletas, cuya *ratio* músculo-grasa es especialmente alta, pero la composición corporal también cambia entre sexos, edades y grupos étnicos.[106, 107] El IMC no distingue entre grasa y masa muscular, y aporta aún menos información sobre la distribución de dicha grasa. Dado que la grasa de distribución central es la más importante para el riesgo cardiovascular, el IMC podría no ser una medida óptima del riesgo asociado al aumento ponderal.[108, 109, 111]

Las técnicas más precisas para medir la composición grasa del cuerpo son también las más sofisticadas.[96] En la actualidad, la tomografía computarizada (TC) y la resonancia magnética (RM) son las más precisas.[110] Sin embargo, son técnicas costosas, que no tienen gran cabida fuera de protocolos de investigación. La imagen por energía dual de absorción de rayos X (*dual-energy X-ray absorptiometry*, DXA) es una alternativa válida, con un margen de error, en comparación con la RM, de un 3%.[112] La tabla 12 resume las ventajas e inconvenientes de distintos métodos para medir adiposidad, entre las que se incluyen medidas de circunferencia de la cintura, la cadera y sus *ratios*.[114, 119 120]

No obstante, el aspecto fundamental de un índice de adiposidad es su grado de asociación con la morbimortalidad de la población. Sin ser perfecto, el IMC ha

demostrado una correlación robusta con el riesgo cardiovascular y la mortalidad en general.[107, 122, 124, 125, 255] El IMC muestra una correlación muy alta con la circunferencia abdominal y la grasa subcutánea.[126] También se correlaciona con un gran número de parámetros cardiovasculares y el porcentaje de grasa corporal.[107]

Más allá de estas asociaciones, la popularidad del IMC justifica también su uso. Las medidas de peso y estatura son fácilmente accesibles y, posiblemente, las únicas que pueden ser autoadministradas con precisión. Además, la mayoría de las personas conocen y comprenden su IMC, y esta circunstancia hace del IMC en una herramienta muy útil en la educación sanitaria.

8.1.8 Epidemiología de la demencia

Se estima que la demencia afecta entre el 5 y el 7% de la población por encima de los 60 años,[128] y que la prevalencia asciende hasta el 45% en la población de más de 85 años.[129] La población mundial está experimentando un aumento progresivo del número total de ancianos y del porcentaje de población envejecida, especialmente en naciones en vías de desarrollo.[128] China, India y Latinoamérica, en particular, pueden experimentar transformaciones demográficas drásticas en los próximos años. La prevalencia de la demencia aumenta con la edad, multiplicándose por 2 cada 5,5 a 7 años. Así, el número de personas afectadas por demencia se estimó en 24,3 millones en 2005,[130] 35,6 millones en 2010,[128] y se calcula que se duplicará para el 2025.[128]

Estos cálculos asumen que no habrá cambios en la incidencia de la demencia.[131] Aunque la prevalencia global esté en aumento, es posible que ciertos grupos y zonas experimenten reducciones en la incidencia. En ese caso, estudiar estas poblaciones aportaría claves críticas en la lucha contra esta dolencia. La investigación sobre cambios seculares en la incidencia de demencia es muy compleja desde el punto de vista metodológico, dados los largos periodos de tiempo que separan distintas cohortes y los cambios que se han producido en los criterios diagnósticos.[131] Es probable que la detección de demencia cada vez sea más precoz, y que se esté extendiendo a pacientes

con otras comorbilidades. Algunos estudios describen estabilidad en la prevalencia de demencia,[132, 133] mientras que otros proponen que hay un descenso en la incidencia.[131]

Los cambios en estimaciones de prevalencia deben relacionarse con los cambios en supervivencia tras el diagnóstico: así, si la supervivencia aumenta pero la prevalencia se mantiene estaremos ante un descenso de incidencia. Un estudio reciente comparó dos cohortes transversales en el área de Estocolmo, Suecia, separadas por intervalos de 20 años, pero diagnosticadas con los mismos criterios.[131] En comparación con la población estudiada en los años 80, la cohorte más reciente tenía una edad media más alta, más años de escolaridad y menor proporción de mujeres. Además, presentaban puntuaciones más altas en la escala MMSE. La prevalencia estandarizada por edad y sexo no varió entre cohortes. Después de controlar por año de nacimiento, la cohorte más reciente presentó un OR menor de diagnóstico de demencia, y este riesgo se vio particularmente reducido entre los varones. Ambas cohortes tuvieron seguimiento: la cohorte del 2001 presentó menor mortalidad para todos los participantes y también para el subgrupo de demencia. Esto implica que la incidencia de demencia está disminuyendo en la región[131].

Otro estudio en dos fases que se llevó a cabo en Zaragoza describió una prevalencia estable en dos cohortes examinadas en los años 90 y 00.[134] La prevalencia ajustada por edad entre los hombres había bajado en la cohorte más reciente, mientras que la mortalidad general de la región se había reducido. Si se asume que la mortalidad también se redujo entre las personas con demencia, esto sugeriría que hubo un descenso de incidencia entre las dos cohortes.[134] La primera cohorte tuvo seguimiento y se disponen de cálculos de incidencia, que fueron 8,6/1 000 personas-año, de las cuales 5,4/1 000 personas-año sufrieron EA. Hasta que se publiquen los seguimientos de la segunda cohorte, estos estudios solo pueden ofrecer medidas indirectas en cambios de incidencia.

Esta disminución aparente en la incidencia podría responder a mejoras en el manejo del riesgo cardiovascular. Es importante señalar que tanto el estudio de Estocolmo como el de Zaragoza encontraron reducción de riesgo entre los varones.[131, 134]

Los esfuerzos iniciales en el tratamiento del riesgo cardiovascular en los años 70 y 80 se centraron en los hombres, que entonces presentaban las incidencias más altas de estas enfermedades.[136] Es posible que los factores de riesgo cardiovascular hayan estado infradiagnosticados e infratratados en las mujeres durante una parte importante de las tres últimas décadas.[136] El interés reciente por la salud cardiovascular de las mujeres quizás haya contribuido a cambiar esta tendencia. Una mejor atención hacia la salud cardiovascular podría acompañarse de una reducción en la incidencia de demencia, también entre las mujeres.

Recientemente se ha descrito una asociación inversa entre demencia y riesgo de neoplasia.[137] Incluso tumores relativamente benignos como los carcinomas de piel no melanocíticos se asocian a una reducción del riesgo de demencia.[138] Tanto el cáncer como la demencia se asocian a la edad avanzada, y podrían representar distintos caminos patológicos en la forma en la que el cuerpo combate el envejecimiento.

8.1.9 Mortalidad en la demencia

Se sabe que las personas con demencia tienen ven reducida su supervivencia, pero existe controversia sobre los factores que pueden influir en su pronóstico.[142-150] La edad, el sexo, el nivel cognitivo en el momento del diagnóstico, la comorbilidad, el tipo de demencia y el lugar de residencia han sido señalados como factores que pudieran contribuir a ese pronóstico.

8.1.9.1 Edad y mortalidad

La edad avanzada aumenta la mortalidad tras un diagnóstico de demencia,[143, 150, 153-155] aunque los años de vida perdidos son lógicamente superiores en sujetos jóvenes.[142] Las enfermedades que causan demencia no son las mismas en edades tempranas y tardías, lo que debe tenerse en cuenta cuando se atribuye la mortalidad a la edad.[156] La DFT, que aparece típicamente en edades más tempranas,[146, 156] también es una de las que presenta mayor mortalidad, especialmente si se asocia a enfermedad de motoneurona.[159] Las

comorbilidades como la diabetes pueden asociarse a un inicio más temprano, y también ser causas independientes de mortalidad.[160]

8.1.9.2 Género y mortalidad

La mayoría de los estudios publicados encuentran una menor mortalidad de la demencia en mujeres.[143, 146, 150, 153, 154, 157, 161-164] Existen excepciones a esta tendencia,[155, 165] y algunos autores encuentran que el efecto del sexo depende del tipo de demencia.[142, 158, 166, 167] Así, por ejemplo, las mujeres con DV[166] o DLB[168] tendrían peor pronóstico que los hombres. En todo caso, dado que tienen un mayor riesgo de demencia y una mayor supervivencia global, las mujeres presentan una mayor proporción de muertes por demencia que los hombres.[150, 153, 157] Al tener menor mortalidad basal, el OR de mortalidad de las mujeres con demencia comparadas con controles sin demencia será más alto que en los hombres, aunque presenten menores tasas de mortalidad cruda.[158]

8.1.9.3 Funcionamiento cognitivo y mortalidad.

El efecto del funcionamiento cognitivo basal está poco aclarado, con unos estudios que encuentran incremento de mortalidad con déficit cognitivo avanzado,[157] pero no moderado, otros detectan una relación con el grado de deterioro cognitivo incluso en estadios leves,[169, 170] y aún otros que no encuentran ninguna asociación con el nivel cognitivo basal[154] ni con la velocidad de deterioro tras el diagnóstico.[163]

8.1.9.4 Tipo de demencia y mortalidad

La mayoría de los estudios describen menor mortalidad en la EA,[142, 146, 150] o no encuentran diferencias con otras demencias[151, 159, 167, 168, 174]. Los estudios previos se han centrado en EA y DV, [150, 161, 166, 169, 177, 178] pero hay pocas comparaciones directas con un espectro más amplio de diagnósticos.[142] Cuando los estudios examinan EA, DV y demencia mixta, en ocasiones encuentran que esta última presenta un riesgo intermedio entre las dos primeras.[166] Los estudios que comparan EA y DLB suelen encontrar mayor

en la DLB,[167, 179] incluso después de controlar por nivel cognitivo.[165] Para otras comparaciones existen menos evidencias. La DLB podría ser más letal que la EPD,[171] que a su vez presenta mayor mortalidad que la EP o la población sana.[181] La DFT parece tener peor pronóstico que otras demencias.[146, 183]

8.1.9.5 Índice de masa corporal y mortalidad

El índice de masa corporal predice mortalidad. [95, 185] La OMS define como normal un IMC entre 18,5 y 24,9 kg/m^2,[95] que se asocia a menor mortalidad en adultos jóvenes.[95] El rango óptimo para personas mayores está menos claro, y se han propuesto puntos de corte de 19 y 23 como guías de *screening* nutricional en estas poblaciones.[185-188] Muchos estudios proponen que el IMC óptimo para una menor mortalidad en edades avanzadas podría situarse en el rango del sobrepeso, según lo define la OMS (25-29,9 kg/m^2),[189-191] o incluso en los primeros tramos de la obesidad (por encima de 30 kg/m^2). Este hallazgo del sobrepeso como factor protector en personas mayores se ha denominado "paradoja de la obesidad"[192] y es el equivalente de la "hipótesis de epidemiología inversa" descrita para otros factores de riesgo cardiovascular.[193 194]

8.1.10 SveDem: Registro Nacional Sueco de Demencia

El registro SveDem se creó en 2007 a partir de una iniciativa de investigadores del *Swedish Brain Power*, con el apoyo de la asociación de autoridades locales y regiones (*Sveriges Kommuner och Landsting*).[212-216] Su objetivo principal es evaluar y mejorar la calidad del cuidado de los pacientes con demencia en toda Suecia, y garantizar su equidad.[217] Los diagnósticos *de novo* se incluyen en un registro informático, junto con datos sobre el proceso diagnóstico,[214, 215, 218] el tratamiento y el cuidado de cada paciente.[213] Los pacientes y los datos incluidos proceden tanto de centros de atención primaria como de unidades especializadas.[212]

Los pacientes se incluyen en el momento en que se establece un diagnóstico de demencia, según los criterios de la ICD-10, y a partir de ahí se programa un seguimiento

anual.[213] La demencia se clasifica en EA, DV, mixta, DLB, EPD, DFT, demencia no especificada y otras demencias (incluyendo cualquier otra causa conocida de demencia no incluida en las categorías previas).[213] Además se recogen edad, sexo, MMSE basal, si el paciente vive solo o acompañado, lugar de residencia (en casa o en una institución), si el paciente trabaja, conduce o tiene permiso de armas, y datos biométricos como estatura y peso. También se incluye el número de fármacos que el paciente consume de forma regular.[222] Esta variable se usa como un indicador de comorbilidad porque ha demostrado ser mejor que otros indicadores farmacológicos en predecir morbimortalidad.[223] Se anotan los tratamientos con antidepresivos, ansiolíticos, hipnóticos, neurolépticos, fármacos de acción cardiovascular, y fármacos específicos para la demencia como los inhibidores de la acetilcolina y antagonistas de N-metil-D-aspartato (NMDA).[213, 215, 217]

El Comité Regional de Ética de Estocolmo aprobó la creación y gestión de SveDem. En el momento del diagnóstico se informa a pacientes y allegados de la existencia del registro, y de que pueden denegar su consentimiento a participar. Existen procedimientos para retirar pacientes del registro. Los datos se archivan de forma anónima y se procesan en el *Uppsala Clinical Trial Center*.[213] Un coordinador examina de forma aleatoria un 10% de las historias clínicas, y valida los datos incluidos en SveDem. Cada unidad que participa en el registro puede acceder con facilidad a estadísticas *on-line* y comparar sus procesos diagnósticos con los de otras unidades.

En 2010, el Ministerio de Sanidad sueco publicó recomendaciones para el diagnóstico y atención a personas con demencia.[228] El proceso diagnóstico básico recomendado en todos los casos incluye una historia clínica estructurada, una entrevista con un informador válido, una evaluación física y psicológica, un estudio cognitivo que como mínimo incluya MMSE y test del reloj, una prueba de neuroimagen y un análisis de sangre que incluya calcio, homocisteína y función tiroidea.[228] Además, estas recomendaciones enfatizan la importancia del diagnóstico temprano y de ofrecer una atención integral a los pacientes con demencia. En Suecia, muchos pacientes son diagnosticados y tratados en centros de atención primaria. En el registro SveDem se han

detectado algunas diferencias entre los procesos diagnósticos de las cohortes de atención primaria y los de la atención especializada (tabla 13).[227]

8.2 OBJETIVOS

8.2.1 Estudio I

1. Describir y comparar las características basales de los sujetos con quejas cognitivas subjetivas (QCS), deterioro cognitivo leve (DCL) y demencia tipo Alzheimer (EA) diagnosticados en una unidad de memoria.
2. Determinar qué factores contribuyen a los diagnósticos de QCS, DCL y EA.

8.2.2 Estudio II

1. Describir las características basales de una gran cohorte nacional de pacientes registrados en Suecia con diagnóstico *de novo* de demencia.
2. Determinar el riesgo de mortalidad relativo de los distintos tipos de demencia.
3. Analizar el riesgo de mortalidad en relación con la edad, el sexo, el funcionamiento cognitivo basal, la institucionalización, vivir solo o acompañado y el número de fármacos consumidos en los pacientes con demencia.

8.2.3 Estudio III

1. Encontrar el rango de índice de masa corporal (IMC) que se corresponde con menor riesgo de mortalidad en pacientes con demencia.
2. Determinar si el rango de IMC asociado a menor mortalidad difiere en hombres y mujeres y en función de la edad.

8.3 HIPÓTESIS

8.3.1 Estudio I

1. Los individuos con quejas cognitivas subjetivas (QCS) difieren en varios aspectos de aquellos con deterioro cognitivo leve (DCL) o enfermedad de Alzheimer (EA).
2. Los sujetos con QCS son más jóvenes y tienen mejor rendimiento cognitivo y menos factores de riesgo cardiovascular que los pacientes con DCL o EA.
3. La prevalencia de enfermedades psiquiátricas es mayor en los sujetos con QCS.
4. Los sujetos con QCS tienen menos atrofia temporal medial que los pacientes con DCL o EA.
5. La prevalencia de apolipoproteína E4 (ApoE4) es menor en los individuos con QCS que en los pacientes con DCL o EA.
6. El patrón de biomarcadores típico de EA en el líquido cefalorraquídeo es menos frecuente en el grupo con QCS.

8.3.2 Estudio II

1. La EA tiene menor riesgo de mortalidad que otros tipos de demencia.
2. La edad avanzada aumenta el riesgo de mortalidad en ambos sexos y en todos los tipos de demencia.
3. El sexo masculino se asocia a un incremento de mortalidad.
4. Los niveles cognitivos más bajos, según la puntuación del *Mini Mental State Examination* (MMSE), se asocian a un riesgo de mortalidad más elevado.

5. La mayor comorbilidad, medida a través del número habitual de fármacos consumidos por el paciente en el momento del diagnóstico, se asocia a mayor riesgo de mortalidad.
6. La institucionalización se asocia a mayor riesgo de mortalidad.
7. Vivir solo se asocia a mayor riesgo de mortalidad.

8.3.3 Estudio III

1. La relación entre el índice de masa corporal (IMC) y el riesgo de mortalidad en pacientes con demencia sigue una distribución en U, con el punto de menor riesgo situado en el IMC correspondiente a la categoría normal o de sobrepeso.
2. Con IMC superiores a $\geq$30 kg/m^2, aparecerá un exceso de riesgo de mortalidad.
3. El IMC asociado con menor riesgo de mortalidad es distinto en hombres y en mujeres.

8.4 MÉTODOS

8.4.1 Estudio I

El primer estudio I utilizó los registros de la base de datos del *Karolinska Memory Clinic*. Los métodos empleados se describen con detalle en la sección correspondiente del artículo. Lo que aquí se recoge es un breve resumen.

8.4.1.1 Karolinska Memory Clinic

La *Karolinska Memory Clinic* forma parte del Departamento de Geriatría del Hospital Universitario Karolinska, Huddinge, y atiende unos 450 pacientes nuevos al año. La valoración de los trastornos cognitivos se lleva a cabo dentro de un marco clínico que

incluye geriatras, psiquiatras, neurólogos, neuropsicólogos, enfermeras, terapeutas ocupacionales y logopedas. Con frecuencia el proceso diagnóstico se completa con distintas pruebas de neuroimagen y análisis del LCR.

Todos los pacientes son evaluados mediante una entrevista, una exploración física y un examen cognitivo con pruebas de *screening* y con otros tests en caso de ser necesarios, incluyendo partes de la *Wechsler Adult Intelligence Scale, Revised* (WAIS-R),[232] distintos tests de memoria,[233-235] *Trail making*,[233] y/o fluencia verbal (Verbal *Fluency test*, FAS).[236] El diagnóstico sigue los estándares de buena práctica clínica, y lo realiza un equipo multidisciplinario haciendo uso de los criterios diagnósticos vigentes para cada entidad clínica. El estudio que nos ocupa recoge datos de pacientes evaluados entre 2007 y 2009. Durante este periodo, el diagnóstico de QCS siguió la clasificación de la ICD-10 ("Z03.3 = observación para un posible trastorno neuro-orgánico") en los casos en los que los pacientes describieron quejas cognitivas que no pudieron objetivarse en los tests.[5] El diagnóstico de DCL siguió los criterios de consenso sobre DCL.[237] Por su parte, el diagnóstico de EA se basó en los criterios de la ICD-10/DSM-IV para demencia y en los criterios de la NINCDS-ADRDA.[5, 238, 239]

En el estudio I se analizaron de forma retrospectiva los 1 154 pacientes evaluados en la *Karolinska Memory Clinic* entre 2007 y 2009. Se excluyeron pacientes con diagnósticos distintos de EA, DCL o QCS. También fueron excluidos del estudio los pacientes con comorbilidades graves que ponían en entredicho el diagnóstico (tales como tumores cerebrales, epilepsia concurrente o metástasis). No se excluyeron pacientes con afecciones comunes, como depresión, ansiedad, insuficiencia cardiaca o insuficiencia renal. Finalmente, se incluyeron un total de 993 pacientes. El comité ético de Estocolmo aprobó este estudio.

Todos los pacientes habían sido estudiados con pruebas de neuroimagen y en 560 casos se había cuantificado la atrofia del lóbulo temporal de forma ciega, mediante la escala Scheltens.[240] En 943 pacientes se analizó la presencia de lesiones de sustancia blanca en tomografía axial computarizada (TC) o en secuencias FLAIR de resonancia

magnética (RM).[241] La presencia de atrofia central se evaluó en 980 pacientes (para más detalles, ver la sección de neuroimagen en el apartado de métodos del artículo I).

Los marcadores de EA del LCR se determinaron en 744 pacientes, y los puntos de corte se fijaron en 400 ng/l, o más, para tau total (t-tau), 80 ng/l, o más, para tau fosforilada (p-tau) y 450 ng/l, o menos, para beta amiloide de 42 residuos (Aβ 42). El genotipo de la apolipoproteina E (ApoE) se analizó en 325 pacientes. La exploración neuropsicológica se describe en la sección de métodos del artículo I. En resumen, se empleó la escala *Mini-Mental State Examination* (MMSE), además de otros tests seleccionados según el perfil clínico del paciente.[233-235] Se registraron asimismo los síntomas psicológicos y conductuales asociados a demencia (BPSD, *behavioral and psychological symptoms associated with dementia*). La presencia de depresión se estableció mediante los datos recogidos en la entrevista clínica y la escala Cornell de depresión en demencia, con un punto de corte de 8.[242]

8.4.1.2 Métodos estadísticos

Las diferencias entre grupos para variables discretas se analizaron con el test de χ^2. Para variables cuantitativas se presentan las medias en cada grupo (EA, DCL y QSC). Las medias de los grupos EA y DCL se compararon con los QSC. En los casos en los que las variables no siguieron una distribución normal, se usaron valores p obtenidos de regresión logística binaria.

A continuación se analizaron las similitudes entre cada paciente de la base de datos y un "tipo EA" definido por el grupo EA de la muestra. Para ello se creó un modelo estadístico en tres pasos. En primer lugar, se probó un gran número de variables, para determinar qué combinación clasificaba mejor a los pacientes de la muestra en EA/no EA (donde "no EA" incluyó pacientes con QCS y DCL). Las mejores variables fueron la edad, el sexo, la puntuación en el MMSE, el cociente Aβ42/t-tau y el valor de p-tau, de modo que el modelo de regresión logística con esa combinación de variables clasificó correctamente al 94,9% de la muestra. En la segunda fase, el modelo se aplicó a cada

paciente, asignando en cada instancia una probabilidad de ser más "similar a EA" (llamada "probabilidad EA" de aquí en adelante). Estas probabilidades se almacenaron como una variable y se usaron como variable resultado en la tercera fase. En este tercer paso, se analizaron modelos independientes para DCL y QCS usando la probabilidad EA como resultado. Así, se fueron introduciendo las variables clínicas una a una en los modelos, en un intento de identificar cuáles de ellas aumentaban la probabilidad de los pacientes de ser clasificados como EA por el modelo. La sección de métodos del artículo I contiene más detalles.

8.4.2 Estudios II y III

Lo que sigue es un breve resumen de los métodos empleados en los estudios II y III. Para más información, se remite al lector a las secciones de métodos de los artículos correspondientes.

8.4.2.1 El registro SveDem de demencia

Los estudios II y III emplean datos de SveDem – el registro sueco de demencia – que recoge pacientes con diagnósticos de demencia *de novo* a nivel nacional. Estos dos estudios incluyen pacientes registrados entre 2008 y 2011 en unidades de memoria. Se excluyeron los pacientes registrados desde los centros de atención primaria, dado que estos centros se unieron más tarde y de forma más dispersa, y que además muestran diferencias en los procedimientos diagnósticos con respecto a los centros de atención especializada (tabla 13).[214] De un total de 15 224 pacientes atendidos en centros especializados, en el estudio II se excluyeron 15 pacientes que tenían datos incompletos en los campos de diagnóstico, edad, sexo o supervivencia (0.1%), de forma que quedaron 15 209 pacientes para los análisis. En el estudio III se requirieron, además, datos completos para el índice de masa corporal (IMC), quedando 11 398 pacientes para el análisis.

En ambos estudios, se incluyeron como variables el tipo de demencia, el sexo, la puntuación basal en el MMSE, la situación de corresidencia (vivir solo o acompañado), el lugar de residencia (en casa, en una institución, o en una institución para personas con demencia) y el número de fármacos consumidos de forma habitual (como variable representativa de comorbilidad[213 223]). Además se incluyeron de forma específica los fármacos de acción cardiovascular, antidepresivos, ansiolíticos, neurolépticos, hipnóticos, inhibidores de la acetilcolinesterasa y antagonistas de NMDA. El IMC se analizó como posible factor de confusión en el estudio II y como variable principal en el estudio III.

8.4.2.2 Estudio II

Se usaron regresiones de Cox para identificar los factores asociados a aumento de riesgo de mortalidad. Los resultados se presentan como cocientes de riesgo (*hazard ratios*—HR) e intervalos de confianza del 95%. La suposición de proporcionalidad de riesgos se comprobó con curvas de Kaplan-Meier y variables tiempo-dependientes. En los casos en los que este supuesto no se cumplía, se calcularon los HR al principio del periodo de observación y al cabo de 1 000 días. Se calcularon las medias y desviaciones estándar (DE) para la estadística descriptiva.

Se crearon modelos crudos (sin ajustar), ajustados por edad y sexo, y ajustados por edad, sexo y medicación. El modelo final se ajustó por sexo, edad (incluida como variable categórica con puntos de corte en 65, 75 y 85), número de fármacos (en categorías 0-1, 2-5, 6-9 y 10 o más) y MMSE (categorías según "falta", "paciente no valorable", MMSE 0-9, 10-19, 20 a 24, y 25 o más). Además, el modelo incluyó lugar de residencia (vivir en casa o en una institución), y si el paciente vivía o no solo. El diagnóstico de demencia se incluyó en el modelo final siguiendo ocho categorías: EA, mixta, DV, DLB, DFT, EPD, otras causas de demencia, y demencia no especificada.

8.4.2.3 Estudio III

Los métodos estadísticos fueron similares a los del estudio II. Para más detalles se remite al lector a la sección de métodos del artículo III. Aquí sigue un resumen de las particularidades de este estudio.

El IMC se exploró usando las categorías de la OMS: bajo peso (IMC debajo de 18,5 kg/m^2), normal (18.5 a 24,9 kg/m^2), sobrepeso (25 a 29,9 kg/m^2), y obesidad (por encima de 30 kg/m^2). Dado que en estudios previos se había encontrado un exceso de mortalidad con IMC en rango normal en personas mayores,[185-187] se incluyó otra categoría siguiendo las guías de la OMS (tabla 11) para definir un grupo de individuos con peso normal pero "delgados" (desde 18,5 a 22,9).

Se emplearon variables de representación lineal por tramos (*splines*) para ajustar mejor la relación entre IMC y mortalidad. Los *splines* son variables concatenadas separadas por puntos de corte (nudos) que el investigador elige. En este caso, se emplearon *splines* lineares, lo que implica que se trató el IMC como una variable continua y que la relación entre IMC y mortalidad se consideró lineal dentro de cada segmento. Se probaron distintos nudos y también se realizó estratificación por grupos de edad y sexo.

8.4.2.4 Consideraciones éticas

El Comité Ético Regional de Estocolmo aprobó la creación y gestión de datos de SveDem. Los estudios basados en SveDem se aprobaron por los comités regionales de Estocolmo (número de permiso 2009/209-31). En el momento del diagnóstico, los pacientes y familiares reciben información oral y/o por escrito sobre SveDem y pueden negarse a participar. Es posible solicitar la retirada de un paciente de SveDem. Para más información sobre SveDem, se puede consultar la página web www.svedem.se. En la figura 1 de la versión en inglés se muestra la nota informativa que se exhibe en las

unidades que registran pacientes en SveDem. Los datos se archivan de forma anónima y se analizan de manera remota.

8.5 RESULTADOS

8.5.1 Estudio I

Los resultados aparecen detallados en al artículo I. Lo que sigue a continuación es un breve resumen.

8.5.1.1 Estadística descriptiva

En este estudio se incluyeron 433 sujetos con quejas cognitiva subjetiva (QCS), 373 con deterioro cognitiva leve (DCL), y 187 con demencia tipo Alzheimer (EA). Las características de estos grupos se muestran en las tablas 1 a 4 del artículo I. Se encontraron diferencias demográficas y clínicas evidentes. En el grupo de QCS los sujetos incluidos fueron más jóvenes, tenían más años de escolaridad y mejor nivel cognitivo (según las puntuaciones del *Mini-Mental State Examination*, MMSE). Además entre los pacientes con QCS hubo mayor proporción de mujeres y más antecedentes familiares de demencia. A cambio, los factores de riesgo cardiovascular fueron menos frecuentes en este grupo. La puntuación media en la escala de atrofia temporal en el grupo de QCS fue 0,98 en el lado derecho y 1,00 en el izquierdo, menor que en los grupos de DCL o EA. Los marcadores de líquido cefalorraquídeo con patrón de EA no fueron tan frecuentes en el grupo de QCS, y el porcentaje de pacientes con uno o más alelos ApoE ε4 fue menor que en el grupo de EA, pero sin diferencias significativas con el grupo DCL. En los pacientes con QCS la puntuación media en la escala de Cornell de depresión en demencia fue 7,8 (desviación estándar 5,8), próxima al punto de corte de 8 que se estableció como límite para depresión y por encima de la puntuación media del grupo con EA pero sin diferencias significativas con el grupo DCL (tabla 2 del artículo I)

8.5.1.2 Modelo de predicción estadístico

Se desarrollaron dos modelos estadísticos para predecir qué características hacían a los pacientes DCL y QCS más parecidos al grupo DA en esta muestra ("probabilidad-DA"). En la tabla 5 del artículo I se observan los resultados de estos modelos. La hipertensión arterial aumentaba en 7% el "probabilidad-DA", mientras que no resultó significativo entre los DCL. El antecedente de ictus reducía el probabilidad-DA en el grupo DCL en un 26%. La puntuación de atrofia temporal aumentaba el probabilidad-DA en el grupo QCS pero lo reducía en el grupo DCL. Las lesiones de sustancia blanca (LSB) se asociaron a una reducción en DCL, pero a un aumento en SCI.

8.5.2 Estudio II

Los resultados detallados de este trabajo pueden verse en la sección correspondiente del artículo III. Se analizaron en total 15 209 pacientes, 59% fueron mujeres. La edad media fue 78,1 años (DE 8,2) y el MMSE medio 21,3 (DE 5,1). Pocos pacientes tenían demencia avanzada según MMSE (tabla 1; artículo II).

La tabla 2 del artículo II muestra diferencias basales entre los distintos tipos de demencia. Un 37% de la muestra había sido diagnosticado de EA, y un 25% de demencia mixta. El seguimiento medio fue de 2,5 años con un total de 4 287 muertes observadas (114 muertes/1 000 persona-año; 95% CI 111 -117). En la tabla 1 se aprecian las tasas de mortalidad en función de las características basales.

Las razones de riesgo (*hazard ratio*, HR) de mortalidad obtenidos de regresiones de Cox se muestran en la tabla 4 del artículo II. Se incluyeron variables tiempo-dependientes para DCL, demencia no especificada y otras demencias dado que presentaban HR no proporcionales. En análisis crudos y ajustados, los hombres presentaron mayor riesgo de mortalidad que las mujeres (tabla 4; artículo II). No hubo interacción entre MMSE y género, o entre género y tipo de demencia. Las diferencias

entre hombres y mujeres permanecieron al estratificar por tipo de demencia, aunque los resultados fueron no significativos para la DFT y la DLB (artículo II).

En los análisis crudos, cada año de edad se asociaba a un exceso de riesgo del 8%. Tras ajustar el análisis, el riesgo aumentaba en cada categoría de edad: en comparación con los pacientes menores de 65, aquellos entre 75 y 84 años tenían un riesgo de mortalidad tres veces mayor, que se hacía seis veces mayor por encima de los 85 años (tabla 4; artículo II).

Empleando al grupo de MMSE igual o superior a 25 como referencia, los pacientes con menor puntuación presentaron aumento de riesgo de muerte. Los pacientes que se consideraron "no evaluables" para MMSE presentaron el riesgo más alto (HR 3,72, 95% CI 3,19-4,35).

Vivir en una institución y tomar más medicación se asociaron a un aumento de riesgo. En cambio, vivir solo no se asoció a un aumento de riesgo estadísticamente significativo (tabla 4; artículo II).

Tal como se puede observar en la figura 2 de la versión inglesa de esta tesis, las curvas Kaplan-Meier de supervivencia muestran que la EA tiene tasas de supervivencia mayores que otras demencias. En análisis Cox no ajustados, el HR más alto se asoció a DV (ver sección de resultados del artículo II). Después de ajustar por edad y sexo, la EPD fue la que presentó mayor riesgo. Cuando se introdujo el número de medicación en el modelo, la DFT pasó a ser la de mayor riesgo (ver figura y resultados del artículo II).

En el modelo ajustado final, todos los otros tipos de demencia presentaron mayor riesgo que la DA, siendo la DFT la de mayor riesgo (HR 1,91; 95% CI 1,52-2,39). La demencia mixta presentó un riesgo intermedio entre la EA y la DV.

En un análisis post-hoc se reanalizó toda la cohorte, incluyendo los pacientes registrados en centros de atención primaria entre los años 2007 y 2012, con un total de

28 704 pacientes. Como se puede comprobar en la tabla 14 (versión en inglés de esta tesis), los HR fueron muy similares a los obtenidos en la cohorte de unidades especializadas.

8.5.3 Estudio III

Los resultados detallados pueden verse en la sección correspondiente del artículo III. Aquí se incluye un breve resumen. El total de pacientes ascendió a 11 398, con un valor medio de IMC de 24,5 (DE 4,3). La tabla 2 del artículo III muestra las tasas de mortalidad de los distintos grupos de IMC.

En los análisis de supervivencia de Cox, los IMC más altos se asociaron a menor riesgo de mortalidad. El grupo de IMC entre 18,5 y 22,9 se tomó como referencia. En comparación con este grupo, el grupo de IMC menor de 18,5 presentó mayor riesgo, mientras que los pacientes de más IMC presentaron un riesgo menor. El riesgo de mortalidad más bajo se observó en el grupo con IMC superior a 30 (HR 0,65; 0,57-0,74 $p<0.001$). Al estratificar los análisis por sexos, el grupo de menor mortalidad correspondió a la categoría con obesidad en los hombres, y a la categoría con sobrepeso en las mujeres (tabla 3; artículo III).

Cuando se usaron *splines* de IMC, cada punto de aumento en la escala de IMC se asoció a un descenso en el riesgo de mortalidad hasta el valor de IMC de 29,9. Los resultados se muestran en la tabla 4 del artículo III. El riesgo de mortalidad descendió un 11% por cada punto incrementado en el IMC para pacientes con IMC por debajo de 22, un 5% por punto para pacientes con IMC entre 22 y 25 y un 3% para pacientes entre 25 y 29,9. Los resultados no fueron significativos en el tramo de IMC mayor de 30. Cuando se retiró el número de fármacos consumidos del modelo, apareció un aumento significativo del riesgo en el tramo de IMC mayor de 30 (HR 1,04; 95% CI 1,00-1,07).

Los análisis con *splines* confirmaron diferencias entre los sexos: los varones presentaron reducciones significativas del riesgo con el aumento del IMC en los grupos

de menos de 18.5 y entre 25 y 30 kg/m^2. En las mujeres, este menor riesgo fue significativo solo hasta el final del rango de la categoría normal (HR 0,94; CI 0,88 to 1,00 tabla 5 y figura A; artículo III).

8.6 DISCUSIÓN

8.6.1 Estudio I

En esta cohorte de la *Karolinska Memory Clinic*, los pacientes con QCS se diferenciaron de aquellos con DCL o EA. Los individuos con QCS eran más jóvenes, tenían menos factores de riesgo cardiovascular y sus puntuaciones del MMSE fueron más altas. Los biomarcadores en el LCR en este grupo presentaron, de media, niveles normales, y el alelo ApoE4 fue menos frecuente que en los pacientes con EA. Los pacientes con QCS refirieron con mayor frecuencia historia familiar de demencia y sus puntuaciones en la escala Cornell de depresión en demencia fueron más altas.

Estas diferencias se podrían justificar por distintos factores. Los clínicos que diagnosticaron a estos pacientes tuvieron acceso a los resultados en LCR y ApoE durante el proceso diagnóstico, de modo que la circularidad del proceso podría haber influido en los diagnósticos. Tradicionalmente, se han atribuido las QCS a cuadros de ansiedad o depresión, así que la mayor prevalencia de historia familiar y mayor puntuación en la escala Cornell podrían encajar en una teoría psicosomática de las QCS. Nuestro estudio no distingue entre síntomas depresivos y un diagnóstico formal de depresión, pero algunos estudios han detectado estos síntomas en el 8 y el 16% de los pacientes mayores.[243] La depresión en edades avanzadas es particularmente resistente al tratamiento, y se asocia a déficits en tests neuropsicológicos. La velocidad de procesamiento y la función ejecutiva parecen particularmente afectadas, lo que conlleva déficits mnésicos secundarios y quejas cognitivas. [244] En nuestro estudio, los pacientes con QCS se diferenciaron en cuanto a la presencia de síntomas depresivos solo de los pacientes con EA y no del grupo con DCL. Esto podría indicar que los pacientes con QCS y DCL experimentan depresión como síntoma reactivo ante la pérdida cognitiva,

demostrando que tienen conciencia de enfermedad que podría en la fase de demencia de la EA. Otra posible explicación es que los síntomas de depresión fueran más difíciles de identificar en pacientes con un deterioro más avanzado.

La interrelación entre la depresión y la demencia es compleja. La depresión en las edades medias de la vida se asocia a un incremento del riesgo de demencia en años posteriores. Por otra parte, la depresión causa déficits cognitivos y, aunque estos presentan un patrón más "subcortical" que la EA, el diagnóstico diferencial puede ser difícil. Para complicar más aún las cosas, los déficits cognitivos asociados a depresión a veces persisten una vez resuelto el episodio depresivo.[244] El ánimo bajo, como síntoma, se asocia a riesgo futuro de DCL de tipo amnésico, y parece interaccionar de forma sinérgica con la presencia de ApoE4.[245] Dos estudios recientes contribuyen a aclarar algunas cuestiones.[246] Ambos se llevaron a cabo en la *Karolinska Memory Clinic* y presentan cohortes similares a la nuestra. El primero comparó el perfil del LCR entre sujetos mayores deprimidos con o sin EA.[243, 246] Este estudio no encontró relación entre biomarcadores de EA y depresión. Sin embargo, apareció una correlación negativa entre síntomas depresivos y los niveles de t-tau) y p-tau. Los pacientes deprimidos eran más jóvenes en este estudio, aunque presentaron puntuaciones análogas en el MMSE.[246] Tal vez en esa cohorte la depresión podría llevar a un diagnóstico más temprano de demencia a través de un aumento de síntomas disejecutivos que el MMSE tendría difícil identificar.[247] Este supuesto podría explicar la edad media más baja y los menores niveles de tau en los sujetos deprimidos.

El otro estudio analizó el grado de atrofia del lóbulo temporal medial en pacientes con QCS, DCL y EA, comparando grupos de pacientes deprimidos y no deprimidos.[243] En la EA los síntomas depresivos se asociaron a menor atrofia temporal, mientras que en pacientes con QCS se asociaron a menores volúmenes del hipocampo. Estos hallazgos podrían indicar que los dos grupos se diferencian en los mecanismos que median la asociación entre el funcionamiento cognitivo y la depresión.[243] Una posibilidad es que, entre los pacientes con EA, la depresión empeore los síntomas cognitivos ocasionando un diagnóstico más temprano. Otra posibilidad es que la depresión requiera conciencia de

enfermedad, que desaparece en pacientes con EA cuando progresa la atrofia temporal. En las QCS, la depresión podría ser una manifestación del proceso neurodegenerativo que tiene lugar en la EA preclínica. Sin duda, estos dos estudios plantean cuestiones intrigantes sobre la interrelación entre depresión y cognición en los distintos estadios del *continuum* de la EA.

La segunda parte de nuestro estudio se basó en un modelo estadístico creado para analizar la probabilidad de presentar un perfil clínico de EA en los participantes de nuestra base de datos. Este modelo se creó en tres pasos: primero, se generó un modelo de regresión logística, que clasificó correctamente a los pacientes en EA/no EA según se definió por su diagnóstico clínico. El mejor modelo para esta clasificación resultó ser aquel que contenía edad, sexo, MMSE, cociente Aβ42/t-tau y p-tau. En el segundo paso se aplicó este modelo a cada individuo de la muestra, asignando a cada uno una probabilidad de tener EA. Esta probabilidad se denominó "probabilidad de EA" y se usó como variable resultado en el último paso. En este tercer paso, todas las variables se introdujeron una a una para determinar cuáles se asociaban a un aumento de la "probabilidad de EA" dentro de este modelo.

Nuestro estudio incluyó una cuantificación de la atrofia temporal medial por parte de un observador experimentado que no tuvo acceso a datos clínicos. Como cabía esperar, los pacientes con QCS tendían a presentar valores normales. Dentro del modelo estadístico, las puntuaciones altas en la escala de atrofia temporal se asociaron a un aumento de la probabilidad de EA en el grupo con QCS. En el grupo con DCL se observó una relación opuesta: cuanto mayor fue el grado de atrofia, menor fue la probabilidad de EA. Dado que los clínicos tuvieron acceso a la neuroimagen (aunque no a las puntuaciones) este resultado se puede, en parte, achacar a la circularidad ya mencionada. Los pacientes del grupo de DCL que presentaban atrofia temporal probablemente presentaron otras características atípicas para EA; de otro modo, habrían sido diagnosticados de EA. Dado que los pacientes con QCS clínicamente estaban más lejos de la demencia, este problema podría ser menos relevante en ese grupo. Los hallazgos en cuanto a la atrofia central y las lesiones de sustancia blanca confluentes fueron similares:

dentro del modelo estadístico, estas variables se asociaron positivamente a "probabilidad de EA" en el grupo con QCS y negativamente en el grupo con DCL.

En este trabajo se examinaron una serie de variables que reflejan riesgo vascular, incluyendo las lesiones de sustancia blanca, los antecedentes de ictus, la hipertensión arterial, o el número total de factores de riesgo cardiovascular. Dentro del modelo, estos factores tendían a asociarse a un incremento de la probabilidad de EA en el grupo con QCS y a un descenso de la misma en el grupo con DCL. Es complicado interpretar estos resultados, puesto que estos grupos difieren en las características basales, tal y como puede observarse en la tabla I del artículo. En todo caso, estos resultados podrían estar reflejando diferencias fundamentales en el diagnóstico diferencial que se establece en cada categoría. Los pacientes con DCL tienen un deterioro demostrado, y su diagnóstico diferencial se plantea entre la EA y otra patología no EA – posiblemente vascular. Aunque los factores de riesgo vascular se asocian con la EA,[248] lo hacen en mayor medida con la patología vascular, y su presencia empujaría el diagnóstico de este grupo en sentido opuesto de la EA. En el grupo de QCS el diagnóstico diferencial se establece fundamentalmente entre una patología neurodegenerativa de cualquier tipo o quejas de origen funcional. Así, en estos pacientes los factores de riesgo cardiovascular hacen al paciente más similar al de EA.

Una de las limitaciones del estudio es su diseño transversal. Solamente un seguimiento longitudinal podría aportar respuestas acerca de la progresión de la atrofia o el deterioro cognitivo en sujetos con QCS y DCL. Existen algunas pruebas de que la relación entre el grosor cortical y la cognición pudiera ser variable. La relación entre biomarcadores en LCR y grosor cortical sigue una relación en U invertida, y los sujetos con cognición normal que presentan valores transicionales en el LCR tienen también mayor grosor de la corteza en regiones temporoparietales y en el *precuneus*.[53] Una explicación es que solo los individuos con cortezas cerebrales constitucionalmente más gruesas pueden permanecer intactos desde el punto de vista cognitivo, aún con indicios de neurodegeración. Otra posibilidad es que el espesor cortical sea dinámico y que evolucione a lo largo del curso de la enfermedad. Estas cuestiones sólo pueden aclararse

con estudios prospectivos.

La selección de los pacientes para este estudio fue oportunista, basándose en los pacientes remitidos a una unidad de memoria. Se trata, por tanto, de una muestra naturalística, que refleja la heterogeneidad de la práctica clínica habitual. Esto explica por qué no se aplicaron todos los tests a todos los pacientes: algunos no los necesitaron, o se negaron a someterse a alguna prueba. La circularidad ocurre cuando hay una dependencia entre variables empleadas para definir grupos al comienzo del estudio y variables analizadas, y es un problema evidente en estudios de este diseño. Para evitarla en lo posible, las valoraciones de las pruebas de neuroimagen se realizaron de forma ciega, aunque los clínicos tuvieron acceso a las imágenes a la hora de hacer el diagnóstico.

La falta de un criterio estandarizado para definir el estado de QCS es un problema en todos los estudios que tratan esta entidad.[31, 61] Siguiendo nuestro diseño naturalístico, solo se excluyeron los pacientes que presentaban comorbilidades graves que ponían en duda el diagnóstico (tales como tumores intracraneales o metástasis). Esta heterogeneidad explica el alto porcentaje de parkinsonismo en el grupo de DCL (21%) y apunta a posible presencia de patología de Lewy o vascular subcortical.

En diversos estudios se han encontrado múltiples diferencias entre los individuos con QCS y la población sana.[31, 33, 50, 51, 53, 60, 61, 63, 64, 70, 249, 250] De hecho, algunos autores sugieren que las QCS pueden ser el primer estadio detectable en la EA.[33, 40, 251] Sin embargo, es difícil identificar qué sujetos presentarán deterioro en el futuro. Las quejas cognitivas con tests neuropsicológicos normales podrían ser particularmente reveladoras en personas con alto nivel educativo, puesto que en ellas el efecto techo de los tests les resta sensibilidad.[60] El grupo con QCS de nuestra muestra tenía un nivel educativo alto, reflejando la composición de la Suecia urbana de su generación. Sin embargo, solo algunos de ellos desarrollarán una enfermedad neurodegerativa y solo el seguimiento puede indicar cuáles serán. Nuestro estudio sigue la línea de los criterios de Dubois [252] y las guías de la NIA, [9] que buscan expandir el diagnóstico de la EA a estadios más tempranos.

8.6.2 Estudio II

El segundo estudio se basa en una cohorte de 15 209 pacientes diagnosticados en unidades de memoria e incluidos en SveDem entre 2008 y 2011. El riesgo de mortalidad para diferentes tipos de demencia y factores de base se calculó empleando razones de riesgo (*hazard ratios*, HR) obtenidas a partir de regresiones de Cox. Los factores asociados con mayor riesgo de mortalidad fueron el sexo masculino, la edad más avanzada, el consumo de una mayor cantidad de de fármacos, la institucionalización, el peor nivel cognitivo (medido por el MMSE) y los diagnósticos de demencia distintos de la EA.

En esta cohorte, los hombres presentaron un riesgo de mortalidad un 56% superior a las mujeres. Este hallazgo está en la línea de estudios previos.[143, 146, 150, 153, 154, 157, 161-164]. Al estratificar por diagnóstico, los hombres continuaron presentando mayor riesgo de mortalidad en todos los tipos de demencia excepto en en la DFT y la DLB, en las cuales las diferencias no fueron significativas. La mayor diferencia entre hombres y mujeres apareció en la EPD, con un 71% de aumento de riesgo en los varones.

Como cabía esperar de estudios previos, la edad más avanzada [143, 150, 153-155] y el menor rendimiento en el MMSE[157, 169] se asociaron a aumento de riesgo de mortalidad. Los pacientes "no evaluables" por MMSE presentaron un riesgo cuatro veces mayor que aquellos con MMSE igual o superior a 25, lo cual revela un efecto suelo de este test.

Nuestro estudio empleó el número de fármacos consumidos de forma habitual como una medida indirecta de la comorbilidad, y su aumento se asoció a un mayor riesgo de mortalidad. El riesgo de mortalidad dependió asimismo del diagnóstico de modo que la EA presentó menor riesgo que cualquier otro tipo de demencia. En análisis crudos, el riesgo más alto se asoció a la DV, y en análisis ajustados la demencia de mayor riesgo fue la DFT (tabla 5; artículo II). Como puede observarse en la tabla 2 del artículo, los pacientes con DFT eran más jóvenes y tomaban menos medicación. La supervivencia en la DFT abarca desde 3[159] a 9,5[93, 175] años según estudios previos. La DFT presenta peor

supervivencia que la EA en la mayoría de los estudios.[146] Aunque es una enfermedad rara, afecta a individuos jóvenes y relativamente sanos y se asocia a un riesgo de mortalidad desproporcionado, lo que subraya la necesidad de redoblar esfuerzos en esta enfermedad.

De acuerdo con la literatura previa, la EA presenta menor mortalidad que otros tipos de demencia,[142, 146, 150] aunque algunos estudios no encuentran diferencias.[142, 146, 150] Pocos estudios comparan un espectro amplio de diagnósticos,[142, 146, 150] y esa es una de las aportaciones fundamentales de nuestro estudio. Como era esperable, la enfermedad mixta entre EA y DV presentó un riesgo intermedio entre estas dos entidades. Dado que las enfermedades cardiovasculares constituyen las primeras causas de mortalidad en los pacientes con demencia (independientemente del diagnóstico), el aumento de riesgo observado en la DV no es sorprendente.[142, 146, 150] En estudios previos se ha encontrado que la EA tiene menor morbilidad asociada que otros tipos de demencia[142, 146, 150], lo que encaja con la menor cantidad de medicación que tomaban los pacientes con EA de nuestra muestra (tabla 2; artículo II).

Salvo excepciones,[180] la mayoría de los estudios publicados describen peor pronóstico para la DLB que para la EA.[167, 179]. En nuestra cohorte, los pacientes con DLB tenían mayor riesgo de mortalidad que la EA. Cuando se introdujo la DLB como categoría de referencia, el riesgo en la EA fue más bajo y no se detectaron diferencias con la EPD o la DV. Las similitudes entre EDP y DCL[82] podrían explicar, en parte, este hallazgo.

La ausencia de un grupo de control cognitivamente intacto es una limitación de este estudio. SveDem es un registro nacional que incluye pacientes diagnosticados de demencia en la práctica clínica habitual, sin un protocolo de estudio para el diagnóstico. Las guías del *Socialstyrelsen*[228] – el ministerio de Sanidad sueco – establecen unos requerimientos básicos para el diagnóstico de demencia. En SveDem, más del 85% de los pacientes cumplen estos criterios.[217]

La naturaleza observacional de este estudio impide hacer inferencias de causalidad. SveDem tiene una cobertura superior al 25% de la incidencia esperada de demencia, pero esta proporción resulta insuficiente para hacer cálculos de incidencia. Sin embargo, ambos estudios incluyeron únicamente pacientes de atención especializada. Dado que la cobertura de SveDem en unidades especializadas es superior al 90%, y dado que éstas registran a la mayoría de sus pacientes, la cobertura para atención especializada sería muy superior al 25%. Nuestro estudio tuvo un seguimiento de 2,5 años de media, quizás insuficiente para detectar cambios en el riesgo de mortalidad a lo largo del tiempo y saber si el riesgo aumenta o disminuye en alguna fase concreta de la enfermedad.

El sesgo de duración aparece en estudios que mezclan casos *de novo* y casos prevalentes, en los que pacientes con enfermedades rápidamente progresivas mueren antes del reclutamiento.[143] La inclusión exclusiva de casos *de novo* en nuestro estudio es uno de sus puntos fuertes, y debería ayudar a controlar este sesgo. La selección de casos atendidos en unidades de memoria tuvo como objetivo aumentar la fiabilidad del diagnóstico, pero podría suponer una limitación si este grupo no fuese comparable al de los pacientes valorados en atención primaria. Cuando se han analizado las diferencias entre ambas cohortes, dentro de SveDem, se ha encontrado que los pacientes de atención primaria son de más edad, tienen más comorbilidad y son evaluados con protocolos diferentes.[214, 227] Para determinar si la exclusión de los centros de primaria podía tener un impacto relevante en los resultados, se procedió a repetir los análisis con todos los pacientes incluidos en SveDem, tanto los de niveles de atención primaria como los de la atención especializada, entre los años 2007 y 2012. Tal y como se muestra en la tabla 14, esta inclusión no alteró los resultados de un modo sustancial. El rango de categorías diagnósticas y el gran número de pacientes son los puntos más fuertes de este estudio. Se trata del mayor estudio prospectivo de su categoría que explora mortalidad en demencia de reciente diagnóstico.

8.6.3 Estudio III

En el artículo III se analiza la relación entre el IMC en el momento del diagnóstico y el riesgo de mortalidad. La cohorte incluyó 11 398 pacientes diagnosticados de demencia entre 2008 y 2011 y que tenían datos sobre IMC basal en los registros de SveDem.

En estudios previos se ha analizado la relación entre IMC y mortalidad en distintos grupos de edad, pero este es el primero que lo que hace en un grupo grande de pacientes con diagnóstico reciente de demencia. El IMC bajo se asoció con un incremento del riesgo de mortalidad en los análisis ajustados. El grupo con obesidad presentó el riesgo de mortalidad más bajo, aunque no se encontraron diferencias significativas entre los grupos con obesidad y sobrepeso. Cuando se analizaron como *splines*, cada punto de aumento en la escala de IMC hasta 29,9 se asoció a una reducción del riesgo de mortalidad (figura 1; artículo III).

Hubo diferencias entre ambos sexos: en mujeres, el punto de menor riesgo se encontró en el grupo con sobrepeso, mientras que los hombres tenían el riesgo más bajo en el rango de obesidad. Además, el análisis con *splines* mostró que el riesgo descendía a medida que ascendía el IMC hasta un IMC de 24,9 en mujeres y 29,9 en hombres.

La composición de la muestra, con pocos pacientes de IMC mayor de 35, hace difícil sacar conclusiones en este grupo. Cuando los análisis por *splines* se repitieron sin ajustar por medicación, apareció un aumento del riesgo para IMC de más de 30, indicando que a partir de este punto podría aparecer comorbilidad – reflejada en la cantidad de medicación – que elevaría el riesgo de mortalidad.

La revisión de la literatura parece indicar que existe una relación compleja entre el IMC y la mortalidad en poblaciones especiales. El IMC asociado a menor mortalidad aumenta con la edad[189, 254, 255] y se sitúa en el rango del sobrepeso en poblaciones ancianas,[190, 191, 255, 256] aunque algunos autores describen una mayor mortalidad en

personas mayores con obesidad.[191, 257, 258] Un estudio encontró que el riesgo era un 17% menor en sujetos con obesidad de más de 75 años comparados con el grupo de peso normal. [189] En nuestro estudio, la reducción del riesgo fue de un 27 y en un 32% en los grupos con sobrepeso y obesidad, respectivamente (tabla 3; artículo III).

Aparentemente, el IMC óptimo para una menor mortalidad es más alto en hombres que en mujeres,[190, 255] aunque no todos los estudios apoyan estas diferencias [191]. Uno de los trabajos sobre la relación entre IMC y mortalidad en la población situaba el punto de menor mortalidad entre 18,5 y 25 para las mujeres de más de 55 años, y entre 25 y 30 para los hombres.[255] Estos datos encajan con los resultados de nuestro estudio. Las causas de estas diferencias entre sexos podrían ser biológicas o sociales,[187, 259, 260] y requieren más investigación.

El hallazgo de una menor mortalidad en presencia de factores tradicionales de riesgo cardiovascular se ha denominado "epidemiología inversa" y se ha descrito en poblaciones con enfermedades crónicas y agudas como el fallo renal, ictus, insuficiencia cardiaca, cáncer o SIDA.[203-205] El mismo concepto aplicado a la obesidad se llama "paradoja de la obesidad" y se ha descrito en poblaciones ancianas. [254, 262, 263]. La novedad de nuestro estudio consiste en describir este fenómeno en pacientes con demencia, pero el efecto en sí se conoce desde principios de la década pasada.[261] Aunque este efecto esté validado por observaciones reiteradas, sus causas siguen generando controversia.[195] Las explicaciones son variadas, desde efectos de sesgo, competición entre distintas causas de mortalidad o diferentes mecanismos biológicos.[194, 262] De hecho, nuestro artículo motivó una carta al editor de Moga et al[262] en la que propuso que los resultados podrían corresponder a sesgo o causalidad inversa. Esto nos permitió contestar con otra carta al editor y continuar este fascinante debate. Moga et al expresaron dudas sobre un posible sesgo de selección, dado que en nuestro artículo original solo se incluyeron pacientes de centros especializados. Como estos autores señalan, el riesgo de mortalidad difiere entre centros: en SveDem, el riesgo de mortalidad es más bajo en la atención primaria que en la especializada (HR 0,45; CI 0,42-0,49) [263]. En la tabla I de nuestra carta al editor [263], pueden verse análisis repetidos en toda la base de datos y en atención primaria, donde el

grupo de pacientes con obesidad presentó menor mortalidad que la categoría de referencia.

Por otra parte, la falta de cumplimentación de datos biométricos en algunas entradas de SveDem supone una limitación para los análisis aunque son difíciles de solventar. No obstante, la categoría de pacientes que carecían de datos de IMC presentó un riesgo de mortalidad muy similar a los de IMC entre 25 y 29,9. Para eliminar el efecto de pacientes en extremos de la escala, se repitieron los análisis de *splines* con los pacientes que tenían valores de IMC entre 20 y 31. Los resultados se muestran en la tabla II de la carta al de respuesta[263]: el mayor IMC siguió asociándose a un menor riesgo de mortalidad.

Otras posibles limitaciones del estudio serían el uso de IMC como marcador nutricional[255] y la falta de seguimiento del IMC. Tal y como se argumentó en la introducción de esta tesis, el IMC está ampliamente disponible y es un parámetro bastante fiable para estimar riesgo cardiovascular y mortalidad[196, 210] Sin embargo, los cambios en el IMC sí que podrían ser más sensibles al pronóstico que una medida estática. En un estudio longitudinal realizado en personas de más de 70 años, tanto aquellos que perdieron como los que ganaron peso experimentaron mayor riesgo de mortalidad que aquellos que mantenían un peso estable.[254]

Otras cuestiones planteadas por Moga et al [262] tienen que ver con la cadena causal entre demencia e IMC: la demencia causa pérdida de peso, y esta pérdida de peso puede preceder al diagnóstico.[264] La naturaleza descriptiva de SveDem impide hacer inferencias de causalidad, pero algunos trabajos aseguran que las intervenciones que logran incrementos de peso en pacientes con demencia se asocian con reducciones en su mortalidad.[210] Los métodos de nuestro estudio no permiten determinar qué mecanismos unen el menor IMC con un mayor riesgo de mortalidad en la demencia, pero esta observación tiene valor independientemente del mecanismo causal. Para un clínico que se enfrenta a un paciente con demencia, la relación causal quizás sea poco relevante: lo que importa es recalcar la importancia de la evaluación nutricional completa en pacientes con

demencia, y subraya la utilidad del IMC como marcador pronóstico.

En un futuro, la realización de estudios longitudinales prospectivos podría determinar si los pacientes con demencia se benefician de IMC más altos que los adultos mayores sin demencia. Se necesitarían, además, estudios de intervención para poder precisar las estrategias a aplicar en este caso. Por el momento, el IMC bajo identifica a un grupo de pacientes con demencia con alto riesgo de mortalidad.

8.7 CONCLUSIONES

1. En la *Karolinska Memory Clinic*, los pacientes con quejas cognitivas subjetivas (QCS) constituyeron un grupo distintivo, con edades más jóvenes que los pacientes con deterioro cognitivo leve (DCL) y demencia tipo Alzheimer (EA), más años de escolaridad, menos factores de riesgo cardiovascular, puntuaciones más altas en el *Mini Mental State Examination* (MMSE), patrones normales en el análisis de los biomarcadores de EA del líquido cefalorraquídeo y volúmenes normales de los lóbulos temporales en las pruebas de neuroimagen. Además la atrofia central generalizada, la atrofia cortical y las lesiones de sustancia blanca fueron menos frecuentes en estos pacientes que en los otros grupos, al igual que el genotipo con alelo ApoE4. Los pacientes con QCS presentaron más síntomas de depresión evaluada por la escala Cornell que los pacientes con EA, aunque no se distinguieron en este aspecto del grupo con DCL.
2. El modelo de regresión logística que incluyó edad, sexo, puntuación en el MMSE, coeficiente Aβ42/t-tau y p-tau clasificó correctamente al 94,9% de la muestra en las categorías correspondientes de QCS, DCL o EA. Dentro de dicho modelo, los factores que directa o indirectamente representaban riesgo cardiovascular tendían a aumentar la probabilidad de EA en el grupo con QCS y a disminuirla en el grupo con DCL, traduciendo quizás diferencias fundamentales en el diagnóstico diferencial que se plantea en cada una de estas dos entidades.

3. Una vez diagnosticada la demencia, el tipo de demencia y otras características basales pueden predecir el riesgo de mortalidad. Los factores asociados con mayor riesgo de mortalidad fueron el sexo masculino, la edad más avanzada, el consumo de una mayor cantidad de fármacos, la institucionalización, el peor nivel cognitivo (medido por el MMSE) y los diagnósticos de demencia distintos de la EA. En los análisis crudos la demencia vascular (DV) presentó el riesgo más alto, mientras que la demencia frontotemporal (DFT) se convirtió en la demencia de mayor riesgo tras ajustar por edad, sexo y medicación. Esto sugiere que la DFT es una enfermedad particularmente letal, teniendo en cuenta que afecta a sujetos jóvenes y relativamente sanos.
4. En los pacientes con demencia, los valores más bajos del índice de masa corporal (IMC) se asociaron a riesgos de mortalidad más elevados. El rango de IMC asociado a menor mortalidad fue dependiente del sexo. El riesgo descendía a medida que se incrementaba el IMC hasta los niveles de 24,9 kg/m^2 en las mujeres y 29,9 kg/m^2 en los hombres.

9. REFERENCES

1. Reisberg B, Ferris SH, Leon MJ. Senile Dementia of the Alzheimer Type: Diagnostic and Differential Diagnostic Features with Special Reference to Functional Assessment Staging. In: Traber J, Gispen W, eds. Senile Dementia of the Alzheimer Type: Springer Berlin Heidelberg, 1985:18-37.
2. Boller F. History of dementia. Handbook of clinical neurology 2008;89:3-13.
3. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. Neurobiol Aging 1998;19:173-189.
4. NIA timeline. Available at: http://www.nia.nih.gov/about/nia-timeline. Accessed 24-07-2013.
5. World Health Organization: The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines. Geneva, World Health Organization, 1992.
6. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263-269.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC, 2000.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC, 2013.
9. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280-292.
10. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22:1689-1707; quiz 1837.
11. Hachinski V, Oveisgharan S, Romney AK, Shankle WR. Optimizing the Hachinski Ischemic Scale. Arch Neurol 2012;69:169-175.
12. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry 1994;57:416-418.
13. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzeimers Dis 2006;9:417-423.
14. Moller HJ, Graeber MB. The case described by Alois Alzheimer in 1911. Historical and conceptual perspectives based on the clinical record and neurohistological sections. Eur Arch Psychiatry and Clin Neurosci1998;248:111-122.
15. Alzheimer A, Forstl H, Levy R. On certain peculiar diseases of old age. Hist Psychiatry 1991;2:71-101.

16. Lopez OL, McDade E, Riverol M, Becker JT. Evolution of the diagnostic criteria for degenerative and cognitive disorders. Curr Opin Neurol 2011;24:532-541.

17. Jack CR, Jr., Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257-262.

18. Visser PJ, Vos S, van Rossum I, Scheltens P. Comparison of International Working Group criteria and National Institute on Aging-Alzheimer's Association criteria for Alzheimer's disease. Alzheimers Dement 2012;8:560-563.

19. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol 2012;123:1-11.

20. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012;8:1-13.

21. Markesbery WR. Neuropathological criteria for the diagnosis of Alzheimer's disease. Neurobiol Aging 1997;18:S13-19.

22. Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 2002;58:1791-1800.

23. Ferreira D, Westman E, Eyjolfsdottir H, et al. Brain Changes in Alzheimer's Disease Patients with Implanted Encapsulated Cells Releasing Nerve Growth Factor. J Alzheimers Dis 2014.

24. Wahlberg LU, Lind G, Almqvist PM, et al. Targeted delivery of nerve growth factor via encapsulated cell biodelivery in Alzheimer disease: a technology platform for restorative neurosurgery. J Neurosurg 2012;117:340-347.

25. Eriksdotter-Jonhagen M, Linderoth B, Lind G, et al. Encapsulated cell biodelivery of nerve growth factor to the basal forebrain in patients with Alzheimer's disease. Dement Geriatr Cogn Disord 2012;33:18-28.

26. Karami A, Vijayaraghavan S, Lind G, et al. Changes in CSF cholinergic biomarkers in response to cell therapy with NGF in patients with Alzheimer´s disease. Alzheimers Dement *In press.*

27. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239-259.

28. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479-486.

29. Galasko D. The diagnostic evaluation of a patient with dementia. Continuum (Minneap Minn) 2013;19:397-410.

30. Mesulam M, Wicklund A, Johnson N, et al. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann Neurol 2008;63:709-719.

31. Garcia-Ptacek S, Eriksdotter M, Jelic V, et al. Subjective cognitive impairment: Towards early identification of Alzheimer disease. Neurologia 2013 pii: S0213-4853:00052-2. doi: 10.1016/j.nrl.2013.02.007

32. Braak E, Griffing K, Arai K, et al. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? Eur Arch Psychiatry Clin Neurosci 1999;249 Suppl 3:14-22.

33. Mistur R, Mosconi L, Santi SD, et al. Current Challenges for the Early Detection of Alzheimer's Disease: Brain Imaging and CSF Studies. J Clin Neurol 2009;5:153-166.

34. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379-2388.

35. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010;9:1118-1127.

36. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry 2000;15:983-991.

37. Andersson C. Predictors of cognitive decline in memory clinic patients. Doctoral thesis. Stockholm, Karolinska Institutet: 2007. Available at: http://publications.ki.se/xmlui/bitstream/handle/10616/37834/thesis.pdf?sequence=1 Accessed 2014-11-02

38. Garcia-Ptacek S, Cavallin L, Kåreholt I, et al. Subjective cognitive impairment: who are they? SCI subjects in our clinical practice. Dement Geriatr Cogn Disord Extra *In press.*

39. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry1982;139:1136-1139.

40. Reisberg B, Gauthier S. Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. Int Psychogeriatr 2008;20:1-16.

41. Reisberg B, Prichep L, Mosconi L, et al. The pre-mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. Alzheimers Dement 2008;4:S98-S108.

42. Bassett SS, Folstein MF. Memory complaint, memory performance, and psychiatric diagnosis: a community study. J Geriatr Psychiatry Neurol 1993;6:105-111.

43. Blazer DG, Hays JC, Fillenbaum GG, Gold DT. Memory complaint as a predictor of cognitive decline: a comparison of African American and White elders. J Aging Health 1997;9:171-184.

44. Gagnon M, Dartigues JF, Mazaux JM, et al. Self-reported memory complaints and memory performance in elderly French community residents: results of the PAQUID Research Program. Neuroepidemiology 1994;13:145-154.

45. Jonker C, Launer LJ, Hooijer C, Lindeboom J. Memory complaints and memory impairment in older individuals. J Am Geriatr Soc1996;44:44-49.

46. Paradise MB, Glozier NS, Naismith SL, et al. Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: a cross-sectional study. BMC Psychiatry 2011;11:108.

47. O'Connor DW, Pollitt PA, Roth M, et al. Memory complaints and impairment in normal, depressed, and demented elderly persons identified in a community survey. Arch Gen Psychiatry 1990;47:224-227.

48. Montejo P, Montenegro M, Fernandez MA, Maestu F. Subjective memory complaints in the elderly: Prevalence and influence of temporal orientation, depression and quality of life in a population-based study in the city of Madrid. Aging Ment Health 2011;15:85-96.

49. Tobiansky R, Blizard R, Livingston G, Mann A. The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. Psychol Med 1995;25:779-786.

50. Geerlings MI, Jonker C, Bouter LM, et al. Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. Am J Psychiatry1999;156:531-537.

51. Jorm AF, Christensen H, Korten AE, et al. Memory complaints as a precursor of memory impairment in older people: a longitudinal analysis over 7-8 years. Psychol Med 2001;31:441-449.

52. Lamar M, Dannhauser TM, Walker Z, et al. Memory complaints with and without memory impairment: the impact of leukoaraiosis on cognition. J Int Neuropsychol Soc 2011;17:1104-1112.

53. Fortea J, Sala-Llonch R, Bartres-Faz D, et al. Cognitively preserved subjects with transitional cerebrospinal fluid Aβ-amyloid 1-42 values have thicker cortex in Alzheimer's disease vulnerable areas. Biol Psychiatry2011;70:183-190.

54. Antonell A, Fortea J, Rami L, et al. Different profiles of Alzheimer's disease cerebrospinal fluid biomarkers in controls and subjects with subjective memory complaints. J Neural Transm 2011;118:259-262.

55. Sachdev PS, Brodaty H, Reppermund S, et al. The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70-90 years. Int Psychogeriatr 2010;22:1248-1264.

56. Amariglio RE, Townsend MK, Grodstein F, et al. Specific subjective memory complaints in older persons may indicate poor cognitive function. J Am Geriatr Soc 2011;59:1612-1617.

57. Gallassi R, Oppi F, Poda R, et al. Are subjective cognitive complaints a risk

factor for dementia? Neurol Sci 2010;31:327-336.

58. Riedel-Heller SG, Matschinger H, Schork A, Angermeyer MC. Do memory complaints indicate the presence of cognitive impairment? Results of a field study. Eur Arch Psychiatry Clin Neurosci 1999;249:197-204.

59. Dufouil C, Fuhrer R, Alperovitch A. Subjective cognitive complaints and cognitive decline: consequence or predictor? The epidemiology of vascular aging study. J Am Geriatr Soc 2005;53:616-621.

60. van Oijen M, de Jong FJ, Hofman A, et al. Subjective memory complaints, education, and risk of Alzheimer's disease. Alzheimers Dement 2007;3:92-97.

61. Abdulrab K, Heun R. Subjective Memory Impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. Eur Psychiatry 2008;23:321-330.

62. Wang PN, Wang SJ, Fuh JL, et al. Subjective memory complaint in relation to cognitive performance and depression: a longitudinal study of a rural Chinese population. J Am Geriatr Soc 2000;48:295-299.

63. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology 2006;67:834-842.

64. van der Flier WM, van Buchem MA, Weverling-Rijnsburger AW, et al. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. J Neurol 2004;251:671-675.

65. Bookheimer SY, Strojwas MH, Cohen MS, et al. Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med 2000;343:450-456.

66. Wishart HA, Saykin AJ, Rabin LA, et al. Increased brain activation during working memory in cognitively intact adults with the APOE epsilon4 allele. Am J Psychiatry 2006;163:1603-1610.

67. Rodda JE, Dannhauser TM, Cutinha DJ, et al. Subjective cognitive impairment: increased prefrontal cortex activation compared to controls during an encoding task. Int J Geriatr Psychiatry 2009;24:865-874.

68. Rodda J, Dannhauser T, Cutinha DJ, et al. Subjective cognitive impairment: functional MRI during a divided attention task. Eur Psychiatry 2011;26:457-462.

69. Barnes LL, Schneider JA, Boyle PA, et al. Memory complaints are related to Alzheimer disease pathology in older persons. Neurology 2006;67:1581-1585.

70. Jorm AF, Masaki KH, Davis DG, et al. Memory complaints in nondemented men predict future pathologic diagnosis of Alzheimer disease. Neurology 2004;63:1960-1961.

71. Visser PJ, Verhey F, Knol DL, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. Lancet Neurol 2009;8:619-627.

72. Rolstad S, Berg AI, Bjerke M, et al. Amyloid-beta42 is associated with cognitive impairment in healthy elderly and subjective cognitive impairment. J Alzheimers Dis 2011;26:135-142.

73. Chetelat G, Villemagne VL, Bourgeat P, et al. Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. Ann Neurol 2010;67:317-324.

74. Chetelat G, Villemagne VL, Pike KE, et al. Larger temporal volume in elderly with high versus low beta-amyloid deposition. Brain 2010;133:3349-3358.

75. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270-279.

76. Teipel SJ, Wegrzyn M, Meindl T, et al. Anatomical MRI and DTI in the diagnosis of Alzheimer's disease: a European multicenter study. J Alzheimers Dis 2012;31 Suppl 3:S33-47.

77. Roman GC. Clinical forms of Vascular Dementia. In: Paul RH, Cohen R, Ott BR, Salloway S, eds. Vascular Dementia: Cerebrovascular Mechanisms and Clinical Management. Totowa, NJ: Humana Press Inc; 2005:7-22.

78. Kling MA, Trojanowski JQ, Wolk DA, et al. Vascular disease and dementias: paradigm shifts to drive research in new directions. Alzheimers Dement 2013;9:76-92.

79. Korczyn AD, Vakhapova V, Grinberg LT. Vascular dementia. J Neurol Sci 2012;322:2-10.

80. Fratiglioni L, Launer LJ, Andersen K, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S10-15.

81. Schneider JA, Bennett DA. Where vascular meets neurodegenerative disease. Stroke 2010;41:S144-146.

82. Aarsland D, Londos E, Ballard C. Parkinson's disease dementia and dementia with Lewy bodies: different aspects of one entity. Int Psychogeriatr 2009;21:216-219.

83. Mok W, Chow TW, Zheng L, et al. Clinicopathological concordance of dementia diagnoses by community versus tertiary care clinicians. Am J Alzheimers Dis Other Demen 2004;19:161-165.

84. Aarsland D, Zaccai J, Brayne C. A systematic review of prevalence studies of dementia in Parkinson's disease. Mov Disord 2005;20:1255-1263.

85. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863-1872.

86. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical

and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113-1124.

87. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004;127:550-560.

88. Szewczyk-Krolikowski K, Tomlinson P, Nithi K, et al. The influence of age and gender on motor and non-motor features of early Parkinson's disease: Initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. Parkinsonism Relat Disord 2014;20:99-105

89. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456-2477.

90. Rascovsky K, Grossman M. Clinical diagnostic criteria and classification controversies in frontotemporal lobar degeneration. Int Rev Psychiatry 2013;25:145-158.

91. Llado A, Sanchez-Valle R, Rey MJ, et al. Clinicopathological and genetic correlates of frontotemporal lobar degeneration and corticobasal degeneration. J Neurol 2008;255:488-494.

92. McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001;58:1803-1809.

93. Garcin B, Lillo P, Hornberger M, et al. Determinants of survival in behavioral variant frontotemporal dementia. Neurology 2009;73:1656-1661.

94. Josephs KA, Knopman DS, Whitwell JL, et al. Survival in two variants of tau-negative frontotemporal lobar degeneration: FTLD-U vs FTLD-MND. Neurology 2005;65:645-647.

95. World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1995;854:1-452.

96. Keys A, Fidanza F, Karvonen MJ, et al. Indices of relative weight and obesity. J Chronic Dis 1972;25:329-343.

97. Froese R. Cube law, condition factor and weight-length relationships: history, meta-analysis and recommendations. J Appl Ichthyol 2006;22:241-253.

98. Galilei G. Dialogues Concerning Two New Sciences. Trans. Crew H, de Salvio A. New York: The Macmillan Company; 1914. Available at http://oll.libertyfund.org/title/753. Accessed 2013-10-22.

99. Farahmand BY, Michaelsson K, Baron JA, et al. Body size and hip fracture risk. Swedish Hip Fracture Study Group. Epidemiology 2000;11:214-219.

100. Nash VA, Geffen AJ. The origin of Fulton's condition factor – setting the record straight. Fisheries 2006;31:236-238.

101. Shingleton A. Allometry: The Study of Biological Scaling. Nature Education Knowledge 2010;3:2.

102. Quételet A. Sur l'homme et le développement de ses facultés ou Essai de physique sociale (A treatease on man and the development of his faculties) Vol2. Brussels: Bachelier, 1835.

103. Cohendy R, Rubenstein LZ, Eledjam JJ. The Mini Nutritional Assessment-Short Form for preoperative nutritional evaluation of elderly patients. Aging (Milano) 2001;13:293-297.

104. Goldbourt U, Medalie JH. Weight-height indices. Choice of the most suitable index and its association with selected variables among 10,000 adult males of heterogeneous origin. Br J Prev Soc Med 1974;28:116-126.

105. Hsu PH, Mathewson FA, Rabkin SW. Blood pressure and body mass index patterns-a longitudinal study. J Chronic Dis 1977;30:93-113.

106. Bergman RN, Stefanovski D, Buchanan TA, et al. A better index of body adiposity. Obesity (Silver Spring) 2011;19:1083-1089.

107. Lichtash CT, Cui J, Guo X, et al. Body adiposity index versus body mass index and other anthropometric traits as correlates of cardiometabolic risk factors. PloS One 2013;8:e65954.

108. Arsenault BJ, Beaumont EP, Despres JP, Larose E. Mapping body fat distribution: a key step towards the identification of the vulnerable patient? Ann Med 2012;44:758-772.

109. Vague J. La différentiation sexuelle: facteur déterminant des formes de l'obesité. (Sexual differentiation: a determinant factor in the types of obesity) Presse Med 1947;55:339-340.

110. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol 2012;85:1-10.

111. Ma X, Zhu S. Metabolic syndrome in the prevention of cardiovascular diseases and diabetes – still a matter of debate? Eur J Clin Nutr 2013;67:518-521.

112. Silver HJ, Niswender KD, Kullberg J, et al. Comparison of gross body fat-water magnetic resonance imaging at 3 Tesla to dual-energy X-ray absorptiometry in obese women. Obesity 2013;21:765-774.

113. Wang N, Zhang X, Xiang YB, et al. Associations of adult height and its components with mortality: a report from cohort studies of 135,000 Chinese women and men. Int J Epidemiol 2011;40:1715-1726.

114. World Health Organization. Waist circumference and waist-hip ratio. Report of a WHO expert consultation. Geneva, World Health Organization: 2008. Available at http://apps.who.int/iris/bitstream/10665/44583/1/9789241501491_eng.pdf. Accessed 2014-11-01.

115. Flegal KM, Shepherd JA, Looker AC, et al. Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults. Am J Clin Nutr 2009;89:500-508.

116. Ludescher B, Machann J, Eschweiler GW, et al. Correlation of fat distribution in whole body MRI with generally used anthropometric data. Invest Radiol 2009;44:712-719.

117. Karcher HS, Holzwarth R, Mueller HP, et al. Body fat distribution as a risk factor for cerebrovascular disease: an MRI-based body fat quantification study. Cerebrovasc Dis 2013;35:341-348.

118. Yamashiro K, Tanaka R, Tanaka Y, et al. Visceral fat accumulation is associated with cerebral small vessel disease. Eur J Neurol 2014;21:667-673

119. Sonmez A, Bayram F, Barcin C, et al. Waist circumference cut-off points to predict obesity, metabolic syndrome, and cardiovascular risk in Turkish adults. Int J Endocrinol 2013;2013:767202.

120. Kar S. Anthropometric, clinical, and metabolic comparisons of the four Rotterdam PCOS phenotypes: A prospective study of PCOS women. J Hum Reprod Sci 2013;6:194-200.

121. Cameron AJ, Magliano DJ, Soderberg S. A systematic review of the impact of including both waist and hip circumference in risk models for cardiovascular diseases, diabetes and mortality. Obes Rev 2013;14:86-94.

122. Snijder MB, Nicolaou M, van Valkengoed IG, et al. Newly proposed body adiposity index (BAI) by Bergman et al. is not strongly related to cardiovascular health risk. Obesity 2012;20:1138-1139.

123. Chang H, Simonsick EM, Ferrucci L, Cooper JA. Validation Study of the Body Adiposity Index as a Predictor of Percent Body Fat in Older Individuals: Findings From the BLSA. J Gerontol A Biol Sci Med Sci 2013.

124. Freedman DS, Blanck HM, Dietz WH, et al. Is the body adiposity index (hip circumference/height$^{(1.5)}$) more strongly related to skinfold thicknesses and risk factor levels than is BMI? The Bogalusa Heart Study. Br J Nutr 2013;109:338-345.

125. Patel AV, Hildebrand JS, Gapstur SM. Body mass index and all-cause mortality in a large prospective cohort of white and black US Adults. PloS One 2014;9:e109153.

126. Shiina Y, Homma Y. Relationships between the visceral fat area on CT and coronary risk factor markers. Intern Med 2013;52:1775-1780.

127. Korpela K, Roos E, Lallukka T, Rahkonen O, et al. Different measures of body weight as predictors of sickness absence. Scand J Public Health 2013;41:25-31.

128. Prince M, Bryce R, Albanese E, et al. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013;9:63-75e62.

129. Fitzpatrick AL, Kuller LH, Ives DG, et al. Incidence and prevalence of

dementia in the Cardiovascular Health Study. J Am Geriatr Soc 2004;52:195-204.

130. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366:2112-2117.

131. Qiu C, von Strauss E, Backman L, et al. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology 2013;80:1888-1894.

132. Hall KS, Gao S, Baiyewu O, et al. Prevalence rates for dementia and Alzheimer's disease in African Americans: 1992 versus 2001. Alzheimers Dement 2009;5:227-233.

133. Rorsman B, Hagnell O, Lanke J. Prevalence and incidence of senile and multi-infarct dementia in the Lundby Study: a comparison between the time periods 1947-1957 and 1957-1972. Neuropsychobiology 1986;15:122-129.

134. Lobo A, Saz P, Marcos G, et al. Prevalence of dementia in a southern European population in two different time periods: the ZARADEMP Project. Acta Psychiatr Scand 2007;116:299-307.

135. Lobo A, Lopez-Anton R, Santabarbara J, et al. Incidence and lifetime risk of dementia and Alzheimer's disease in a Southern European population. Acta Psychiatr Scand 2011;124:372-383.

136. Wenger NK. Women and coronary heart disease: a century after Herrick: understudied, underdiagnosed, and undertreated. Circulation 2012;126:604-611.

137. Musicco M, Adorni F, Di Santo S, et al. Inverse occurrence of cancer and Alzheimer disease: a population-based incidence study. Neurology 2013;81:322-328.

138. White RS, Lipton RB, Hall CB, Steinerman JR. Nonmelanoma skin cancer is associated with reduced Alzheimer disease risk. Neurology 2013;80:1966-1972.

139. Dorsey ER, George BP, Leff B, Willis AW. The coming crisis: obtaining care for the growing burden of neurodegenerative conditions. Neurology 2013;80:1989-1996.

140. Olesen J, Gustavsson A, Svensson M, et al. The economic cost of brain disorders in Europe. Eur J Neurol 2012;19:155-162.

141. World Health Organization. Media Center. Dementia. Fact sheet N°362. Available at: http://www.who.int/mediacentre/factsheets/fs362/en/. Accessed 2014-02-11.

142. Brodaty H, Seeher K, Gibson L. Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. Int Psychogeriatr 2012;24:1034-1045.

143. Wolfson C, Wolfson DB, Asgharian M, et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med 2001;344:1111-1116.

144. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. Int J Geriatr Psychiatry 2001;16:751-761.

145. Koller D, Kaduszkiewicz H, van den Bussche H, et al. Survival in patients with incident dementia compared with a control group: a five-year follow-up. Int Psychogeriatr 2012;24:1522-1530.

146. Steenland K, MacNeil J, Seals R, Levey A. Factors affecting survival of patients with neurodegenerative disease. Neuroepidemiology 2010;35:28-35.

147. Rait G, Walters K, Bottomley C, et al. Survival of people with clinical diagnosis of dementia in primary care: cohort study. BMJ 2010;341:c3584.

148. Lonnroos E, Kyyronen P, Bell JS, et al. Risk of death among persons with Alzheimer's disease: a national register-based nested case-control study. J Alzheimers Dis 2013;33:157-164.

149. Zhao Q, Zhou B, Ding D, et al. Prevalence, mortality, and predictive factors on survival of dementia in Shanghai, China. Alzheimer Dis Assoc Disord 2010;24:151-158.

150. Aguero-Torres H, Fratiglioni L, Guo Z, et al. Mortality from dementia in advanced age: a 5-year follow-up study of incident dementia cases. J Clin Epidemiol 1999;52:737-743.

151. Skillback T, Farahmand B, Bartlett JW, et al. CSF neurofilament light differs in neurodegenerative diseases and predicts severity and survival. Neurology 2014.

152. Garcia-Ptacek S, Farahmand B, Kareholt I, et al. Mortality risk after dementia diagnosis by dementia type and underlying factors: a cohort of 15,209 patients based on the Swedish Dementia Registry. J Alzheimers Dis 2014;41:467-477.

153. Ganguli M, Dodge HH, Shen C, et al. Alzheimer disease and mortality: a 15-year epidemiological study. Arch Neurol 2005;62:779-784.

154. Xie J, Brayne C, Matthews FE. Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up. BMJ 2008;336:258-262.

155. Brookmeyer R, Corrada MM, Curriero FC, Kawas C. Survival following a diagnosis of Alzheimer disease. Arch Neurol 2002;59:1764-1767.

156. Koedam EL, Pijnenburg YA, Deeg DJ, et al. Early-onset dementia is associated with higher mortality. Dement Geriatr Cogn Disord 2008;26:147-152.

157. Aevarsson O, Svanborg A, Skoog I. Seven-year survival rate after age 85 years: relation to Alzheimer disease and vascular dementia. Arch Neurol 1998;55:1226-1232.

158. Ostbye T, Hill G, Steenhuis R. Mortality in elderly Canadians with and without dementia: a 5-year follow-up. Neurology 1999;53:521-526.

159. Kang SJ, Cha KR, Seo SW, et al. Survival in Frontotemporal Lobar

Degeneration in a Korean Population. Alzheimer Dis Assoc Disord 2010.

160. Zilkens RR, Davis WA, Spilsbury K, et al. Earlier age of dementia onset and shorter survival times in dementia patients with diabetes. Am J Epidemiol 2013;177:1246-1254.

161. Bruandet A, Richard F, Bombois S, et al. Alzheimer disease with cerebrovascular disease and vascular dementia: clinical features and course compared with Alzheimer disease. J Neurol Neurosurg Psychiatry 2009;80:133-139.

162. Knopman DS, Rocca WA, Cha RH, et al. Survival study of vascular dementia in Rochester, Minnesota. Arch Neurol 2003;60:85-90.

163. Rountree SD, Chan W, Pavlik VN, et al. Factors that influence survival in a probable Alzheimer disease cohort. Alzheimers Res Ther 2012;4:16.

164. Jagger C, Clarke M, Stone A. Predictors of survival with Alzheimer's disease: a community-based study. Psychol Med 1995;25:171-177.

165. Stubendorff K, Hansson O, Minthon L, Londos E. Differences in survival between patients with dementia with Lewy bodies and patients with Alzheimer's disease – measured from a fixed cognitive level. Dement Geriatr Cogn Disord 2011;32:408-416.

166. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Survival following dementia onset: Alzheimer's disease and vascular dementia. J Neurol Sci 2005;229-230:43-49.

167. Magierski R, Kloszewska I, Sobow TM. The influence of vascular risk factors on the survival rate of patients with dementia with Lewy bodies and Alzheimer disease. Neurol Neurochir Pol 2010;44:139-147.

168. Williams MM, Xiong C, Morris JC, Galvin JE. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology 2006;67:1935-1941.

169. Villarejo A, Benito-Leon J, Trincado R, et al. Dementia-associated mortality at thirteen years in the NEDICES Cohort Study. J Alzheimers Dis 2011;26:543-551.

170. Barclay LL, Zemcov A, Blass JP, Sansone J. Survival in Alzheimer's disease and vascular dementias. Neurology 1985;35:834-840.

171. Jellinger KA, Wenning GK, Seppi K. Predictors of survival in dementia with lewy bodies and Parkinson dementia. Neurodegener Dis 2007;4:428-430.

172. Olichney JM, Galasko D, Salmon DP, et al. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. Neurology 1998;51:351-357.

173. Xie SX, Forman MS, Farmer J, et al. Factors associated with survival probability in autopsy-proven frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry 2008;79:126-129.

174. Hodges JR, Davies R, Xuereb J, et al. Survival in frontotemporal dementia. Neurology 2003;61:349-354.

175. Hu WT, Parisi JE, Knopman DS, et al. Clinical features and survival of 3R and 4R tauopathies presenting as behavioral variant frontotemporal dementia. Alzheimer Dis Assoc Disord 2007;21:S39-43.

176. Matsui Y, Tanizaki Y, Arima H, et al. Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama study. J Neurol Neurosurg Psychiatry 2009;80:366-370.

177. Hier DB, Warach JD, Gorelick PB, Thomas J. Predictors of survival in clinically diagnosed Alzheimer's disease and multi-infarct dementia. Arch Neurol 1989;46:1213-1216.

178. Rockwood K, Wentzel C, Hachinski V, et al. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology 2000;54:447-451.

179. Hanyu H, Sato T, Hirao K, et al. Differences in clinical course between dementia with Lewy bodies and Alzheimer's disease. Eur J Neurol 2009;16:212-217.

180. Walker Z, Allen RL, Shergill S, et al. Three years survival in patients with a clinical diagnosis of dementia with Lewy bodies. Int J Geriatr Psychiatry 2000;15:267-273.

181. de Lau LM, Schipper CM, Hofman A, et al. Prognosis of Parkinson disease: risk of dementia and mortality: the Rotterdam Study. Arch Neurol 2005;62:1265-1269.

182. Nunnemann S, Last D, Schuster T, et al. Survival in a German population with frontotemporal lobar degeneration. Neuroepidemiology 2011;37:160-165.

183. Roberson ED, Hesse JH, Rose KD, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. Neurology 2005;65:719-725.

184. Stubendorff K, Aarsland D, Minthon L, Londos E. The impact of autonomic dysfunction on survival in patients with dementia with Lewy bodies and Parkinson's disease with dementia. PLoS One 2012;7:e45451.

185. Volkert D, Berner YN, Berry E, et al. ESPEN Guidelines on Enteral Nutrition: Geriatrics. Clin Nutr 2006;25:330-360.

186. Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci 2001;56:M366-372.

187. Socialstyrelsen. Näring för god vård och omsorg. En vägledning för att förebygga och behandla undernäring. (Nutrition for good health and social care. Guidelines to prevent and treat malnourishment). Stockholm, 2011.

188. Cereda E, Pedrolli C, Zagami A, et al. Body mass index and mortality in institutionalized elderly. J Am Med Dir Assoc 2011;12:174-178.

189. Janssen I. Morbidity and mortality risk associated with an overweight BMI in older men and women. Obesity (Silver Spring) 2007;15:1827-1840.

190. Flicker L, McCaul KA, Hankey GJ, et al. Body mass index and survival in

men and women aged 70 to 75. J Am Geriatr Soc 2010;58:234-241.

191. Kvamme JM, Holmen J, Wilsgaard T, et al. Body mass index and mortality in elderly men and women: the Tromso and HUNT studies. J Epidemiol Community Health 2012;66:611-617.

192. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol 2009;66:336-342.

193. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009;53:1925-1932.

194. Kopple JD. The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. Am J Clin Nutr 2005;81:1257-1266.

195. Levin NW, Handelman GJ, Coresh J, et al. Reverse epidemiology: a confusing, confounding, and inaccurate term. Semin Dial 2007;20:586-592.

196. Martin-Ponce E, Santolaria F, Aleman-Valls MR, et al. Factors involved in the paradox of reverse epidemiology. Clin Nutr 2010;29:501-506.

197. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 2004;43:1439-1444.

198. Anand N, Chandrasekaran SC, Alam MN. The malnutrition inflammation complex syndrome-the micsing factor in the perio-chronic kidney disease interlink. J Clin Diagn Res 2013;7:763-767.

199. Garcia-Ptacek S, Faxen-Irving G, Cermakova P, et al. Body mass index in dementia. Eur J Clin Nutr 2014 doi: 10.1038/ejcn.2014.199

200. Stevens J, Cai J, Pamuk ER, et al. The effect of age on the association between body-mass index and mortality. N Engl J Med 1998;338:1-7.

201. Landi F, Onder G, Gambassi G, et al. Body mass index and mortality among hospitalized patients. Arch Int Med 2000;160:2641-2644.

202. Huang JC, Chen SC, Su HM, et al. Performance of the Framingham risk score in patients receiving hemodialysis. Nephrology (Carlton) 2013;18:510-515.

203. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, Wu DY. Reverse epidemiology: a spurious hypothesis or a hardcore reality? Blood Purif 2005;23:57-63.

204. Guder G, Frantz S, Bauersachs J, et al. Reverse epidemiology in systolic and nonsystolic heart failure: cumulative prognostic benefit of classical cardiovascular risk factors. Circ Heart Fail 2009;2:563-571.

205. Andersen KK, Olsen TS. Body Mass Index and Stroke: Overweight and Obesity Less Often Associated with Stroke Recurrence. J Stroke Cerebrovasc Dis 2013.

206. Kalantar-Zadeh K. What is so bad about reverse epidemiology anyway?

Semin Dial 2007;20:593-601.

207. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-2207.

208. Liu Y, Coresh J, Eustace JA, et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. JAMA 2004;291:451-459.

209. Albanese E, Taylor C, Siervo M, et al. Dementia severity and weight loss: a comparison across eight cohorts. The 10/66 study. Alzheimers Dement 2013;9:649-656.

210. Faxen-Irving G, Basun H, Cederholm T. Nutritional and cognitive relationships and long-term mortality in patients with various dementia disorders. Age Ageing 2005;34:136-141.

211. Garcia-Ptacek S, Kareholt I, Farahmand B, et al. Body-Mass Index and Mortality in Incident Dementia: A Cohort Study on 11,398 Patients From SveDem, the Swedish Dementia Registry. J Am Med Dir Assoc 2014; 15:447.e1-7

212. Eriksdotter M, Farahmand B, Edlund AK for the stiring committee. SveDem – Svenska Demensregistret – 2012 årsrapport (SveDem – Swedish Dementia Registry – 2012 yearly report [Swedish]). SveDem: 2013. Accesible at: http://www.ucr.uu.se/svedem/index.php/om-svedem/arsrapporter. Accessed 2014-11-01.

213. Johnell K, Religa D, Eriksdotter M. Differences in Drug Therapy between Dementia Disorders in the Swedish Dementia Registry: A Nationwide Study of over 7,000 Patients. Dement Geriatr Cogn Disord 2013;35:239-248.

214. Wimo A, Religa D, Spangberg K, et al. Costs of diagnosing dementia: results from SveDem, the Swedish Dementia Registry. Int J Geriatr Psychiatry 2013;28:1039-44.

215. Religa D, Spangberg K, Wimo A, et al. Dementia diagnosis differs in men and women and depends on age and dementia severity: data from SveDem, the Swedish Dementia Quality Registry. Dement Geriatr Cogn Disord 2012;33:90-95.

216. Nordstrom P, Religa D, Wimo A, et al. The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease. Eur Heart J 2013;34:2585-91

217. Eriksdotter M, Edlund AK, for the stiring committee. SveDem – Svenska Demensregistret – 2011 årsrapport (SveDem – Swedish Dementia Registry – 2011 yearly report [Swedish]). SveDem: 2012. Available at http://www.ucr.uu.se/svedem/index.php/om-svedem/arsrapporter. Accessed 2014-11-02

218. Fereshtehnejad S M RD, Westman E, Aarsland D, Lökk J, Eriksdotter M. Comparison of dementia with Lewy Bodies with Parkinson's disease dementia

in the Swedish Dementia Quality Registry (SveDem). Neuropsychiatric Disease and Treatment Journal 2013:9:927-935.

219. Eriksdotter M, for the stiring committee. SveDem – Svenska Demensregistret – 2013 årsrapport (SveDem – Swedish Dementia Registry – 2013 yearly report [Swedish]). SveDem: 2014. *Pending release.*
220. Socialdepartementet. På väg mot en god demensvård. Samhällets insatser för personer med demenssjukdomar och deras anhöriga. (Department of Health. Towards good care in dementia. Societies resources for persons with dementia and their relatives [Swedish]). Socialdepartement, DS:2003:47. Accessible at: http://www.regeringen.se/sb/d/108/a/421. Accessed 2014-11-01.
221. World Health Organization. Dementia: A Public Health Priority. Albany, NY: World Health Organization, 2012.
222. FASS – Vårdpersonal (Swedish Drug Index for healthcare professionals [Swedish]). Available at: http://www.fass.se/LIF/startpage?5. Accessed 28/11/2013.
223. Schneeweiss S, Seeger JD, Maclure M, et al. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol 2001;154:854-864.
224. Fereshtehnejad SM, Johnell K, Eriksdotter M. Anti-dementia drugs and co-medication among patients with Alzheimer's disease : investigating real-world drug use in clinical practice using the Swedish Dementia Quality Registry (SveDem). Drugs Aging 2014;31:215-224.
225. SveDem. About SveDem. Available at: http://www.ucr.uu.se/svedem/index.php/about-svedem. Accessed 2014-11-01
226. Eriksson H, Fereshtehnejad SM, Falahati F, et al. Differences in routine clinical practice between early and late onset Alzheimer's disease: data from the Swedish Dementia Registry (SveDem). J Alzheimers Dis 2014;41:411-419.
227. Modéer IN. Diagnosis and treatment of Alzheimer´s disease in specialist units compared to primary care [Master]. Stockholm, Karolinska University: 2014
228. Socialstyrelsen. Nationella riktlinjer för vård och omsorg vid demenssjukdom 2010 (Swedish National Board of Health and Welfare. National Guidelines for the Care of Cases of Dementia 2010 [Swedish]). Socialstyrelsen: 2010. Accesible at http://www.socialstyrelsen.se/lists/artikelkatalog/attachments/18012/2010-5-1.pdf. Accessed 2014-11-01.
229. Falahati F, Religa D, Wahlund LO, et al . The use of MRI, CT and lumbar puncture in dementia diagnostics, data from the SveDem registry. Dement Geriatr Cogn Dis. *In press.*
230. Fereshtehnejad SM, Cermakova P, Aarsland D, et al. Comorbidity Profile in Dementia with Lewy Bodies versus Alzheimer's Disease: A linkage study between the Swedish dementia registry and the Swedish National Patient

Registry. Alzheimers Res Ther, *In press*

231. Cermakova P, Fereshtehnejad SM, Johnell K, et al. Cardiovascular medication burden in dementia disorders: a nationwide study of 19,743 dementia patients in the Swedish Dementia Registry. Alzheimers Res Ther 2014;6:34.

232. Bartfai A, Wechsler D. Wechsler adult intelligence scale revised. Stockholm: Psykologiförlaget, 1994.

233. Reitan RWD. The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation. Tucson: Neuropsychology Press, 1993.

234. Schmidt, M. Rey auditory verbal learning test - a handbook. Los Angeles: Western Psychological Services, 1996.

235. Lezak M. Neuropsychological assessment, 3rd ed: Oxford University Press, 1995.

236. Fernaeus SE, Almkvist O. Word production: Dissociation of two retrieval modes of semantic memory across time. J Clin Exp Neuropsychol 1998;20:137-143.

237. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240-246.

238. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: Author.

239. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-944.

240. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992;55:967-972.

241. Inzitari D, Pracucci G, Poggesi A, et al. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. BMJ 2009;339:b2477.

242. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. Biol Psychiatry1988;23:271-284.

243. Enache D, Cavallin L, Lindberg O, et al. Medial Temporal Lobe Atrophy and Depressive Symptoms in Elderly Patients With and Without Alzheimer Disease. J Geriatr Psychiatry Neurol 2014.

244. Weisenbach SL, Boore LA, Kales HC. Depression and cognitive impairment in older adults. Curr Psychiatry Rep 2012;14:280-288.

245. Caracciolo B, Backman L, Monastero R, et al. The symptom of low mood in the prodromal stage of mild cognitive impairment and dementia: a cohort

study of a community dwelling elderly population. J Neurol Neurosurg Psychiatry 2011;82:788-793.

246. Kramberger MG, Jelic V, Kareholt I, et al. Cerebrospinal Fluid Alzheimer Markers in Depressed Elderly Subjects with and without Alzheimer's Disease. Dement Geriatr Cogn Disord Extra 2012;2:48-56.

247. Juby A, Tench S, Baker V. The value of clock drawing in identifying executive cognitive dysfunction in people with a normal Mini-Mental State Examination score. CAMJ 2002;167:859-864.

248. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819-828.

249. Rami L, Fortea J, Bosch B, et al. Cerebrospinal fluid biomarkers and memory present distinct associations along the continuum from healthy subjects to AD patients. J Alzheimers Dis 2011;23:319-326.

250. Cherbuin N, Sargent-Cox K, Easteal S, et al. Hippocampal Atrophy is Associated with Subjective Memory Decline: The PATH Through Life Study. Am J Geriatr Psychiatry 2014 pii: S1064-7481(14)00225-5

251. Getsios D, Blume S, Ishak KJ, et al. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. Alzheimers Dement 2012;8:22-30.

252. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734-746.

253. Faxen-Irving G, Fereshtehnejad SM, Falahati F, et al. Body Mass Index in Different Dementia Disorders: Results from the Swedish Dementia Quality Registry (SveDem). Dement Geriatr Cogn Disord Extra 2014;4:65-75.

254. Dahl AK, Fauth EB, Ernsth-Bravell M, et al. Body mass index, change in body mass index, and survival in old and very old persons. J Am Geriatr Soc 2013;61:512-518.

255. Freedman DM, Ron E, Ballard-Barbash R, et al. Body mass index and all-cause mortality in a nationwide US cohort. Int J Obes 2006;30:822-829.

256. Luchsinger JA, Patel B, Tang MX, et al. Body mass index, dementia, and mortality in the elderly. J Nutr Health Aging 2008;12:127-131.

257. Masters RK, Reither EN, Powers DA, et al. The Impact of Obesity on US Mortality Levels: The Importance of Age and Cohort Factors in Population Estimates. Am J Public Health 2013;103:1895-901

258. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. Obes Rev 2007;8:41-59.

259. Kim JH, Choi SH, Lim S, et al. Sarcopenia and obesity: gender-different relationship with functional limitation in older persons. J Korean Med Sci 2013;28:1041-1047.

260. Friedmann JM, Elasy T, Jensen GL. The relationship between body mass

index and self-reported functional limitation among older adults: a gender difference. J Am Geriatr Soc 2001;49:398-403.

261. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? J Am Coll Cardiol 2002;39:578-584.

262. Moga DC, Abner EL, Brouwer ES. Dementia and "Obesity Paradox": Is This for Real or Are We Missing Something? An Epidemiologist's Perspective. J Am Med Dir Assoc 2014 pii: S1525-8610(14)00367-3.

263. Garcia-Ptacek S, Farahmand, B. Cuadrado, M.L. et al. Dementia and Obesity Paradox: Reply to the Letter by Dr. Moga et al. J Am Med Dir Assoc. *In press.*

264. Hanson LC, Ersek M, Lin FC, Carey TS. Outcomes of feeding problems in advanced dementia in a nursing home population. J Am Geriatr Soc 2013;61:1692-1697.

10. ARTICLES

ARTICLE I

Garcia-Ptacek S, Cavallin L, Kåreholt I, Kramberger MG, Winblad B, Jelic V, Eriksdotter M. **Subjective cognitive impairment: who are they? SCI subjects in our clinical practice.** Dement Geriatr Cogn Dis Extra (Accepted for publication, *In press*).

EXTRA
Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2014;4:419–430
DOI: 10.1159/000366270
Published online: November 11, 2014

1664–5464/14/0043–0419$39.50/0
www.karger.com/dee

Karger
Open access

Original Research Article

Subjective Cognitive Impairment Subjects in Our Clinical Practice

Sara Garcia-Ptacek[a, b, i, j] Lena Cavallin[c, f] Ingemar Kåreholt[e, g]
Milica Gregoric Kramberger[d, h] Bengt Winblad[h] Vesna Jelic[a, b]
Maria Eriksdotter[a, b]

[a]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, [b]Department of Geriatric Medicine, Karolinska University Hospital, [c]Department of Clinical Science, Intervention and Technology, and [d]Karolinska Institutet Alzheimer Disease Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, [e]Aging Research Center, Karolinska Institutet and Stockholm University, and [f]Department of Radiology, Karolinska University Hospital, Stockholm, and [g]Institute for Gerontology, School of Health Sciences, Jönköping University, Jönköping, Sweden; [h]Department of Neurology, University Medical Centre, Ljubljana, Slovenia; [i]Department of Neurology, Hospital Clínico San Carlos, and [j]Department of Medicine, Universidad Complutense de Madrid, Madrid, Spain

Key Words
Alzheimer's disease · Dementia · Mild cognitive impairment

Abstract
Background: The clinical challenge in subjective cognitive impairment (SCI) is to identify which individuals will present cognitive decline. We created a statistical model to determine which variables contribute to SCI and mild cognitive impairment (MCI) versus Alzheimer's disease (AD) diagnoses. ***Methods:*** A total of 993 subjects diagnosed at a memory clinic (2007–2009) were included retrospectively: 433 with SCI, 373 with MCI and 187 with AD. Descriptive statistics were provided. A logistic regression model analyzed the likelihood of SCI and MCI patients being diagnosed with AD, using age, gender, Mini-Mental State Examination score, the ratio of β-amyloid 42 divided by total tau, and phosphorylated tau as independent variables. ***Results:*** The SCI subjects were younger (57.8 ± 8 years) than the MCI (64.2 ± 10.6 years) and AD subjects (70.1 ± 9.7 years). They were more educated, had less medial temporal lobe atrophy (MTA) and frequently normal cerebrospinal fluid biomarkers. Apolipoprotein E4/E4 homozygotes and apolipoprotein E3/E4 heterozygotes were significantly less frequent in the SCI group (6 and 36%) than in the AD group (28 and 51%). Within the regression model, cardiovascular risk factors, confluent white matter lesions, MTA and central atrophy increased

Sara Garcia-Ptacek
Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Section for Clinical Geriatrics
Novum plan 5, SE–141 86 Stockholm (Sweden)
E-Mail sara.garcia-ptacek@ki.se

ARTICLE II

Garcia-Ptacek S, Farahmand B, Kåreholt I, Religa D, Cuadrado ML, Eriksdotter M. **Mortality risk after dementia diagnosis by dementia type and underlying factors: a cohort of 15209 patients based on the Swedish Dementia Registry**. J Alzheimers Dis 2014;41:467-77.

Journal of Alzheimer's Disease 41 (2014) 467–477
DOI 10.3233/JAD-131856
IOS Press

Mortality Risk after Dementia Diagnosis by Dementia Type and Underlying Factors: A Cohort of 15,209 Patients based on the Swedish Dementia Registry

Sara Garcia-Ptacek[a,b,1,*], Bahman Farahmand[a,1], Ingemar Kåreholt[c,d], Dorota Religa[e,f], Maria Luz Cuadrado[b,g] and Maria Eriksdotter[a,e]

[a]*Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden*
[b]*Department of Medicine, Universidad Complutense, Madrid, Spain*
[c]*Aging Research Center, Karolinska Institutet and Stockholm University, Stockholm, Sweden*
[d]*Institute of Gerontology, School of Health Sciences, Jönköping University, Jönköping, Sweden*
[e]*Department of Geriatric Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden*
[f]*Division of KI-ADRC, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden*
[g]*Neurology Department, Hospital Clínico San Carlos, Madrid, Spain*

Handling Associate Editor: Alberto Villarejo

Accepted 2 February 2014

Abstract.
Background: Knowledge on survival in dementia is crucial for patients and public health planning. Most studies comparing mortality risk included few different dementia diagnoses.
Objectives: To compare mortality risk in the most frequent dementia disorders in a large cohort of patients with an incident diagnosis, adjusting for potential confounding factors.
Methods: 15,209 patients with dementia from the national quality database, Swedish Dementia Registry (SveDem), diagnosed in memory clinics from 2008 to 2011, were included in this study. The impact of age, gender, dementia diagnosis, baseline Mini-Mental State Examination (MMSE), institutionalization, coresidency, and medication on survival after diagnosis were examined using adjusted hazard ratios (HR) with 95% confidence intervals (CI).
Results: During a mean follow-up of 2.5 years, 4,287 deaths occurred, with 114 (95% CI 111–117) deaths/1,000 person-years. Adjusted HR of death for men was 1.56 (95% CI 1.46–1.66) compared to women. Low MMSE, institutionalization, and higher number of medications were associated with higher HR of death. All dementia diagnoses demonstrated higher HR compared to Alzheimer's disease, with vascular dementia presenting the highest crude HR. After adjusting, frontotemporal dementia had the highest risk with a HR of 1.91 (95% CI 1.52–2.39), followed by Lewy body dementia (HR 1.64; 95% CI 1.39–1.95), vascular dementia (HR 1.55; 95% CI 1.42–1.69), Parkinson's disease dementia (HR 1.47; 95% CI 1.17–1.84), and mixed Alzheimer's disease and vascular dementia (HR 1.32; 95% CI 1.22–1.44).

[1]Authors responsible for statistical analysis.

*Correspondence to: Sara Garcia-Ptacek, Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Section for Clinical Geriatrics, Novum plan 5, 141 86 Stockholm, Sweden. Fax: +46 858585470; E-mail: saragptacek@gmail.com.

ISSN 1387-2877/14/$27.50

ARTICLE III

García-Ptacek S, Kåreholt I, Farahmand B, Cuadrado ML, Religa D, Eriksdotter M. **Body-mass index and mortality in incident dementia: a cohort study on 11,398 patients from SveDem, the Swedish Dementia Registry.** J Am Med Dir Assoc 2014;15:447.e1-7.

NOTICE: this is the author's version of a work that was accepted for publication in *Journal of the American Medical Directors Association*. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in J Am Med Dir Assoc 2014;15:447.e1-7. doi: 10.1016/j.jamda.2014.03.001

Body-mass index and mortality in incident dementia: a cohort study on 11398 patients from SveDem, the Swedish dementia registry.

Sara Garcia-Ptacek MD[1,2,3], Ingemar Kåreholt PhD[4, 5], Bahman Farahmand PhD[1], Maria Luz Cuadrado PhD[3, 6], Dorota Religa MD PhD[2,7], Maria Eriksdotter MD, PhD[1, 2]

[1]Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Clinical Geriatrics, Karolinska Institutet, Novum plan 5, 141 86 Stockholm, Sweden

[2] Department of Geriatric Medicine, Karolinska University Hospital, Stockholm, 141 86 Stockholm, Sweden

[3] Department of Medicine and Universidad Complutense de Madrid, 28040 Madrid, Spain

[4]Aging Research Center (ARC), Karolinska Institutet and Stockholm University, Gävlegatan 16, 8tr, 11330 Stockholm, Sweden

[5]Institute for Gerontology, School of Health Sciences, Jönköping University, 553 18 Jönköping, Sweden

[6]Neurology department Hospital Clinico San Carlos, prof Martin Lagos s/n 28040 Madrid, Spain and Department of Medicine, Universidad Complutense de Madrid, 28040 Madrid, Spain

[7]Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division for Neurogeriatrics, Karolinska Institutet, Novum plan 5, 141 86 Stockholm, Sweden

Abstract:

Background: Body-Mass Index (BMI) is used worldwide as an indirect measure of nutritional status and has been shown to be associated with mortality. Controversy exists over the cut-points associated with lowest mortality, particularly in older populations. In patients suffering from dementia, information on BMI and mortality could improve decisions about patient care.

Objectives: To explore the association between BMI and mortality risk in an incident dementia cohort.

Design: Cohort study based on SveDem, the Swedish quality dementia registry; 2008-2011.

Setting: specialist memory clinics; Sweden.

Participants: 11.398 incident dementia patients with data on BMI (28.190 person-years at risk for death).

Main outcome measures: Hazard ratios (HR) and 95% confidence intervals (CI) for mortality associated with BMI were calculated controlling for age, sex, dementia type, results from Mini-Mental State Examination, and number of medication. BMI categories and linear splines were employed.

Results: Higher BMI was associated with decreased mortality risk, with all higher BMI categories showing reduced risk relative to patients with BMI 18.5 to 22.9 kg/m2, while underweight patients (BMI under 18.5kg/m2) displayed excess risk. When explored as splines, increasing BMI was associated with decreased mortality risk up to BMI 30 kg/m2. Each point increase in BMI resulted in an 11% mortality risk reduction in patients with BMI under 22 kg/m2, 5% reduction when BMI was 22-24.9 kg/m2, and 3% risk reduction among overweight patients. Results were not significant in the obese weight range. Separate examination by sex revealed a reduction in mortality with increased BMI up to BMI 29.9 kg/m2 for men and 24.9 kg/m2 for women.

Conclusion: Higher BMI at the time of dementia diagnosis was associated with a reduction in mortality risk up to and including the overweight category for the whole cohort and for men, and up to the normal weight category for women.

1. Introduction:

Body-mass index (BMI) is a useful biometric measure and predicts mortality in a number of populations[1,2]. The World Health Organization (WHO) defines normal BMI as 18.5-24.9 kg/m2^2 which correlates with lower morbidity among young adults.[3] However, there is some indication that older adults might benefit from higher BMIs,[4-8] and BMI cut-points between 19 and 23 have been used to guide nutritional screening in this population. [1,7,9,10] Controversy exists over the BMI associated with lowest mortality among older individuals, which could lie in the overweight range of BMI as defined by the WHO (25-29.9 kg/m2).[4,6,8] This finding of excess weight, traditionally considered detrimental to health, being protective in older populations has been termed the "obesity paradox".[11]

The relationship between body weight and cognition is complex. Overweight and obese patients have demonstrated better cognitive performance than normal weight individuals in some instances[12]. Patients with dementia have, on average, lower BMIs than their peers since dementia

causes weight loss.[13] A reduction in BMI can predict dementia[14] and predates onset by at least a decade.[15,16] However, higher BMI at middle-age has been shown to increase the risk of dementia in later decades,[11,17] indicating that there is a positive relationship between BMI and dementia that is reversed in old age. The intermediate prodromic stages of the disease are the most difficult to analyze. Among women, being overweight correlates with development of Alzheimer's dementia (AD) even at older ages.[18] Methodological differences between studies in follow-up and design might contribute to these apparent contradictions. Also important is the difficult distinction between BMI as a possible causal factor for dementia and changes in BMI linked to preclinical disease. The overlap between these two factors is especially important in neurodegenerative processes such as AD in which pathological changes begin decades before diagnosis while uncertainty remains about the early course of the disease.

In patients already suffering from dementia, lower BMI has been correlated with increased mortality[19] and severity of cognitive impairment.[13] Since malnutrition is a contributing factor in death by dementia,[19,20] baseline BMI at diagnosis could contribute to predicting mortality and influence decisions on patient care.

The SveDem national incident dementia registry was created in 2007 to improve quality and equality of care for dementia patients throughout Sweden. To date, it includes more than 90% of all new dementia diagnoses made in specialist memory clinics nationwide[21]. The aim of this study is to describe mortality risk relative to BMI, to examine whether lower BMI is associated with higher mortality and determine the BMI corresponding with lowest mortality risk in our dementia population.

2. Patients and methods:

SveDem is a nationwide Swedish quality registry that includes more than 28.000 incident dementia patients to date. Patients meeting ICD-10 [22] criteria for dementia, diagnosed at either memory clinics or primary care are included in the database together with data on height and weight, age, gender, medication and results from diagnostic work-up[23,24] including baseline Mini-Mental State Examination (MMSE). Number of medication at diagnostic work-up, ie approximately at the time of diagnosis, is used as a proxy for comorbidity, since it has been shown to be better than other medication-based comorbidity scores at predicting morbi-mortality [24,25]. Dementia diagnoses are coded as Alzheimer's Disease (AD), Vascular Dementia (VaD), mixed AD and VD (mixed), Lewy Body Disease (LBD--McKeith criteria[26]), Parkinson's-Disease Dementia (PDD--Movement Disorder Society Task Force criteria [27]), Fronto-temporal dementia (FTD--Lund-Manchester criteria[28]), unspecified dementia (where diagnosis is not ascertained) and other dementia types (grouping alcohol related dementias and rare dementia disorders). The national guidelines published by the Swedish National Board of Health and Welfare[29] recommend an established basal dementia work-up for patients with suspicion of dementia: in SveDem, this basic work-up is completed in over 85% of cases[30], with

testing expanded if necessary. Quality control is performed by random cross-checks of histories and entries[30]. Changing diagnoses within the first year of follow-up are about 5%. Based on estimates of dementia incidence in Sweden, SveDem captured around 25% of all new diagnoses in 2011, with a coverage for specialist memory clinics of 93%[30]. SveDem is collated with the national population registry to record deaths.

For this study, we selected patients included in SveDem who had received a dementia diagnosis from a specialist memory clinic between 2008 through 2011 and for whom complete data on BMI, dementia diagnosis, age and sex was available. Primary care was excluded because of more irregular inclusion in the registry and differences in diagnostic process compared to specialist care. Patients were followed up until death, as entered in the national population registry, or end of follow-up in February 2013. Of a total of 15.224 patients registered in this period, 11.413 patients had data on BMI. Of these, 15 (0.1%) patients were excluded because of incomplete information on diagnosis, age, gender or time of death. This left 11.398 patients included in analysis.

2.1. Statistical analyses:

Prospective analyses to identify the relationship between BMI and mortality risk were calculated using Cox proportional hazards regression models and are shown as hazard ratios (HR) of death with 95% confidence intervals (CI). Kaplan-Meier survival curves were employed for a visual confirmation that the assumption of proportional hazards was met. Person-time at risk was calculated individually for all patients from dementia diagnosis to date of death or end of follow-up, on February 2013. Means and standard deviations are provided when appropriate. SPSS version 21 was used for computations.

BMI was explored in categories according to WHO guidelines defining underweight as BMIs under 18.5 kg/m2, normal between 18.5 to 24.9 kg/m2 , overweight from 25 to 29.9 kg/m2 and obese over 30 kg/m2. Because of the previous literature supporting excess risk even in moderately thin older adults[1,9,10,31] and in order to better represent the distribution of our cohort, we also employed the additional WHO cut-off point within the normal range, creating a group for "slim" individuals from 18.5 to 22.9 BMI and another "normal" group, from 23 to 24.9. In order to determine the BMI corresponding to lowest mortality and to better represent the correlation in case of a J or U shaped distribution, piecewise linear representation variables (splines) were used. Linear splines are a series of concatenated variables separated by pre-defined cut points (knots) and designed so that within each interval BMI is explored as a continuous variable. In this way, linearity is only assumed within each interval within the scale while at the same time retaining some of the statistical power of the original continuous variable. Different cut points were explored to capture the shape of the distribution. Because the BMI of lowest mortality was suspected to be different for women and men, stratified analyses by sex were also performed. Since age might modify the effect of BMI on mortality, the

cohort was divided into age tertiles (cut points at age 76 and 83) and analyses repeated in these separate groups.

All estimates were adjusted for age, gender, MMSE, dementia diagnosis and number of medication at diagnostic work-up. A quadratic term was entered for age, since it fitted the mortality distribution best. Gender was treated as a dichotomous variable. MMSE score was classified as not assessable, severe (0-9), moderate (10-19), mild (20-24), and slight impairment (25 and over). Dementia diagnosis was entered as eight diagnostic categories (AD, VaD, mixed, LBD, PDD, FTD, unspecified and other). Number of medication was categorized as 0-1, 2-5, 6-9, and 10 or more habitual drugs at time of diagnostic workup.

Standard protocol approvals and patient consent: The data collection and analysis procedures were approved by the regional ethics committee in Stockholm (approval number 2009/209-31). Patients and caretakers were informed orally and in writing about SveDem, and could decline participation and withdraw consent at any time. Data was collected locally and entered into the web-based database, and coded and anonymized before statistical analysis.

3. Results:

A total of 11398 patients were included and followed-up for an average of 2.5 years (28190 person-years at risk [PYAR]). 3162 deaths were observed (112 deaths per 1000 PYAR). Characteristics of study subjects and mortality are presented in table 1. Mortality for different BMI groups are presented in table 2.

BMI presented a normal distribution with a mean of 24.5 (SD 4.3). The highest mortality rate was observed in the group with BMI under 18.5 (199 deaths PYAR) while the lowest rate occurred in the BMI +30 group (86 deaths PYAR; table 2).

Higher BMI was associated with decreased mortality risk. The slim category (18.5-22.9kg/m2) was used as reference for comparisons, since it was the group with highest number of individuals. In crude analysis, compared to this reference, all other groups except the underweight presented significantly decreased mortality risk. Results remained significant after adjusting and are shown in table 3. The lowest hazard ratio corresponded to the obese BMI +30 group (HR 0.68; 0.59-0.78 $p<0.001$) followed by the overweight 25-29.9 group (HR 0.73; 95% CI 0.66-0.85) and normal 23-24.9 (HR 0.81; 95% CI 0.73-0.89). The underweight BMI under 18.5 group presented excess risk compared to the slim group (HR 1.60; 95% CI 1.39-1.84 $p<0.001$). The lowest mortality risk occurred in the BMI + 30 category for the whole database and for men, while it occurred in the overweight category for women. The analyses were repeated with and without adjusting for number of medication (used as a proxy for comorbidity), without substantial changes in the results. When compared with the obese category, there was significant excess risk in the underweight, slim and normal 23-24.9 categories, with no significant differences with the overweight category (data not shown). When the

sample was split into age tertiles, the BMI +30 category continued to present the lowest HR for mortality, except in the oldest age group in which the obese and overweight categories had similar HR (table 3).

A number of splines were created, joined by cut points or knots. Between each knot, BMI is represented as a continuous variable. When explored as splines, each point increase in BMI was associated with reduced mortality risk up to, and including, the overweight category. Several knots were examined, following WHO guidelines or the Swedish National Board of Health and Welfare. A number of very small splines (spanning only 0.5 points, 1 point or 2 points in BMI) were also tested: due to smaller sample sizes, these were most often non-significant, but they did provide a guideline of how the distribution behaved. Finally, cut points at 18.5, 22, 25 and 30 kg/m2 were chosen: these correspond to the WHO cut-points for underweight, normal weight and obesity[32], with an additional cut-point at BMI 22 which is suggested by the Swedish National Board of Health and Welfare for screening for malnutrition in population over 70[9]. Adjusted results are given in table 4, but were not substantially different from crude results. For patients with BMI under 22, each point increase in BMI was associated with 11% less mortality risk, while it was associated with 5% decreased risk in the 22-25 category, and 3% in the overweight 25-30 category. No significant results were obtained in the obese category. Analyses were rerun controlling for all variables except medication: in this case, growing mortality risk was demonstrated with each point increase in BMI in the obese category (HR 1.04; 95% CI 1.00-1.07).

Stratified by sex, men presented a significant reduction in risk with increasing BMI in the 25-30 group, while for women, decreased risk was present and significant up to, and including, the normal BMI range but not in the overweight or obese categories (table 4). Figure 1a shows results for men and women.

To examine whether the relationship between mortality and BMI was influenced by age, spline analyses were repeated separately on the different age tertiles. Adjusted results are represented in figure 1b. Because of the smaller sample sizes, only splines with knots set at 23 and 30 were used. Probably due to this smaller sample size, results were often not significant in individual splines and categories. Increased BMI was associated with decreased mortality risk in all age categories in the lowest BMI spline (BMI under 23). In the intermediate weight spline (BMI 23-30) a significant, protective effect was detected only in the youngest age group (p=0.003). In the BMI +30 spline, a trend towards increased risk with higher BMI was detected in the youngest and oldest age groups (HR 1.05; 95%CI 0.99-1.10 p=0.071 and HR 1.05; 95% CI 0.98-1.12 p=0.145, respectively). The interaction between the linear splines and age were tested. The difference between the youngest and oldest age groups was significant (p=0.010). This indicates that, compared to the youngest age group, the association between BMI and mortality was weaker in the oldest age group (figure 1b).

4. Discussion:

In our large national incident dementia cohort, low BMI was associated with increased mortality after adjusting for age, gender, MMSE, dementia diagnosis and medication at the beginning of the diagnostic workup. The lowest mortality risk was observed in the obese group, with no significant differences in mortality risk between the obese and overweight categories. In spline analysis, each point increase in BMI resulted in decreased mortality risk up to the end of the overweight category (BMI 29.9). Results were not significant in the BMI +30 spline, possibly due to an absence of covariation between BMI and mortality within this group (the lower horizontal section of a J-shaped curve**).** Furthermore, our sample contained less obese patients (N=1168) and few with BMI over 35 (n=233). Since it is precisely these patients who could present higher mortality from adiposity-related conditions[2,33], the composition of our sample might not have been ideal to demonstrate excess mortality at the higher end of the obesity spectrum. The lowest mortality was observed in the obese weight range in men, while it occurred in the overweight weight range for women. As is shown in figure 1a, when men and women are considered separately, the point of lowest risk for both genders seems to lie around BMI 30 kg/m2 but the risk for women flattens out at lower BMIs than it does for men. This suggests that men benefit from the reduction of mortality risk associated with higher BMI well into the overweight range.

Previous literature suggests that optimal BMI might be lower for women[5,6], although some studies contradict this finding[8]. One publication reported lowest mortality between BMI 18.5-25 among healthy women over 55, and between 25-30 among men[5]. In SveDem, the lowest mortality was observed at lower BMIs in women than in men. Social and biological reasons might motivate this finding. Obesity is linked to sedentary habits, which have a greater negative impact on women than on men[6]. The relationship between BMI, body fat and sarcopenia is different for men and women[34]. Higher BMIs have been correlated with enhanced risk of functional impairment, but increased risk is apparent at lower BMIs in women than in men[35]. On average, muscle mass percentage is greater in men, so body composition, for the same BMI, differs between genders[34]. Sarcopenia predicts frailty in older individuals and increases the risk of death[36], but relative sarcopenia, calculated by dividing muscle mass by weight, could be more relevant in women[34,37], placing obese women with low muscle mass at particular risk.

The appropriateness of BMI as a measure of adiposity in the elderly has been questioned.[5] BMI does not distinguish between fat and lean mass and biometric indexes including waist girth have also been proposed[38]. However, BMI remains widely available and easy to assess: even if other measures of nutritional status prove to be more precise, BMI still remains a valuable option in many settings. Fluctuations in BMI, rather than a single static measure, might predict prognosis better[19,39]. Increased risk was demonstrated for patients over 70 who either lost or gained weight[40]. Others have shown that interventions that succeed in producing weight gain in advanced dementia are associated

with a reduction in mortality.[19] Supplementation might increase survival in older adults[1,7] and it is reasonable to suppose that maintaining a good nutritional status could reduce mortality, particularly in dementia.

The optimal BMI for lowest mortality remains contentious[33] but appears to increase with age[4,5,40], with previous studies indicating that it lies in the overweight range in older populations[4-6,8,40]. Some even suggest that obese older individuals either do not have excess mortality risk compared to those who are normal-weight[40], or even display lower mortality[4,41]. However, others find a mortality increase among the obese[8,42,43]. In a study among people over 55, the optimal BMI for lowest mortality was 18.5-30[5]. In another population sample over 65, compared to those with normal BMI mortality risk was 11% lower in overweight patients and 13% lower in the obese category[4]. This protective effect was accentuated in the +75 subgroup, where mortality risk was 27% lower in the obese group[4]. This compares to our finding of 27% and 32% lower mortality risk for the whole cohort in the overweight and obese groups respectively (table 3). Other studies have found the lowest mortality in the overweight range of BMI for population over 65,[8] and 70 to 75 years of age[6]. In our cohort, the BMI for minimum mortality was comparable across age groups but the whole cohort was older than in previous studies, with an average age of 79. Thus, the finding of lowest mortality in the obese category fits well within previous literature.

It is difficult to disentangle the role of comorbidities, which could be responsible for some of the excess mortality detected in lower weight groups.[5,7] Overweight and obesity[4] have been linked to comorbidity, so controlling for said comorbidity may artificially reduce the risk associated with higher BMIs. However, one study showed that overweight elderly presented lower mortality, without increased risk for most stroke, cancer or myocardial infarction, although diabetes risk did increase.[4] In our study, the number of medication at the beginning of diagnostic work-up was used as a proxy for comorbidity. Models run without controlling for number of medication continued to show the obese category presenting lowest mortality, but spline analyses demonstrated significant excess risk for each point increase in BMI after BMI 30. No substantial changes were evident in other splines or BMI categories in models with and without number of medication. This suggests that the protective effect seen at lower weights is not altered by controlling for medication, but that a proportion of the increasing risk after BMI 30 might be mediated by comorbidity. With our current data, it is impossible to determine if this comorbidity could be obesity related.

Numerous studies indicate that cardiovascular risk factors such as high blood pressure and BMI are protective in some populations.[6,39,44-46] This phenomenon has been termed the "reverse epidemiology hypothesis",[6,39,44-46] or the "obesity paradox" when concerning BMI[47], and has been observed in the elderly,[6,44,46] as well as in patients on maintenance hemodialysis,[45] heart failure,[48] stroke[47], malignancies and AIDS.[45] The explanations for this phenomenon are varied, ranging from bias to the presence of competing hazards or different biological mechanisms[49]. Few studies have

examined the influence of BMI and mortality after dementia diagnosis[19] and population studies with older cohorts can be expected to contain a significant percentage of persons with dementia and other conditions in which reverse epidemiology applies.

With our current data, it is impossible to know what mechanisms link lower BMIs to higher mortality risk in our incident dementia cohort, but examining the characteristics of populations in which reverse epidemiology has been described might provide some insight. These populations all present low life-expectancies in which the deleterious effect of conventional cardiovascular risk factors may not have time to materialize.[40,45] In essence, low BMI might identify patients with strong competing hazards that would supersede cardiovascular risk[49]. Additionally, these populations display high prevalence of malnutrition which is thought to be an important contributor to death.[45,49,50] Malnutrition is linked to inflammation (malnutrition-inflammation syndrome complex-MISC) and through it to atherosclerosis and congestive heart failure,[51] and has been blamed for the disproportionally high mortality rates (mostly cardiovascular) observed among renal failure patients.[45,51] Indeed, in a study examining the association between cholesterol level and mortality in dialysis patients, a reverse epidemiology phenomenon was observed only in those in which MICS was evident, while the normal epidemiological observation of higher cholesterol linked to higher mortality appeared in patients who did not have MISC[52]. Another study among institutionalized elderly found that those with BMI under 21 presented higher cardiovascular, as well as all-cause, mortality.[7] Coincidentally, all of the above are also causes for sarcopenia[53], and low grade inflammation has been independently associated with Alzheimer's disease and with involuntary weight loss in the elderly[54]. Furthermore, since malnutrition is a contributing factor for death in dementia,[20] and since dementia causes weight loss[13], the ideal weight range may be higher in subjects with dementia than among the general old population. Further research is needed to determine the causes of the association between lower BMI and higher mortality in populations with dementia. A longitudinal prospective study comparing cohorts with dementia and controls would be needed to confirm whether patients with dementia benefit from higher BMIs than their cognitively-intact peers, and markers of inflammation would be important to explore. Further research is needed to optimize nutritional strategies for persons with dementia. For now, low BMI serves as a clinical marker that identifies patients with dementia at higher mortality risk.

2. Conclusion:

In our large nationwide incident dementia cohort, increased BMI was associated with reduced mortality risk. This remained true up to BMIs 25 to 29.9 kg/m2 for men and up to 24.9 kg/m2 for women and confirms existing literature suggesting that older populations might fare better with higher body weight. The reduction in mortality risk may be accentuated in dementia, where malnutrition is a common contributor to death. In the future, studies evaluating fluctuations in BMI and nutritional interventions among patients suffering from dementia might help determine nutritional guidelines for

this population.

Acknowledgements: the authors are grateful to the national Swedish Dementia Registry (SveDem, www.svedem.se) for providing data for this study. This study was supported financially by the Swedish Brain Power network (http://swedishbrainpower.se), the Swedish Associations of Local Authorities and Regions, Alzheimerfonden, the Swedish Research Council (Dorota Religa N 523-2012-2291) and Svenska Läkaresällskapet. Sponsors did not participate in study design or interpretation of data. Author contributions: Sara García-Ptacek contributed to the conception and design of the present article, statistical analysis and interpretation of data, drafted the manuscript and is the guarantor of the work. Ingemar Kåreholt and Bahman Farahmand contributed to conception and design of the article, statistical analysis and interpretation of data, revised the manuscript for intellectual content, as well as approved the final version. Maria Luz Cuadrado: contributed to interpretation of data, revised the manuscript for intellectual content, and approved the final version. Dorota Religa: contributed to conception and design of the article, data acquisition, interpretation of data, revised the manuscript for intellectual content and approved the final version. Maria Eriksdotter: contributed to the conception and design of the work, data acquisition, interpretation of data, critical revision of the manuscript for intellectual content and final approval of the published version.

1. Volkert D, Berner YN, Berry E, et al. ESPEN Guidelines on Enteral Nutrition: Geriatrics. *Clin Nutr* 2006;25(2):330-360.

2. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series 854. Geneva: World Health Organization.

3. Kivimaki M, Ferrie JE, Batty GD, et al. Optimal form of operationalizing BMI in relation to all-cause and cause-specific mortality: the original Whitehall study. *Obesity (Silver Spring)* 2008;16(8):1926-1932.

4. Janssen I. Morbidity and mortality risk associated with an overweight BMI in older men and women. *Obesity (Silver Spring)* 2007;15(7):1827-1840.

5. Freedman DM, Ron E, Ballard-Barbash R, et al. Body mass index and all-cause mortality in a nationwide US cohort. *Int J Obes (Lond)* 2006;30(5):822-829.

6. Flicker L, McCaul KA, Hankey GJ, et al. Body mass index and survival in men and women aged 70 to 75. *J Am Geriatr Soc. 2010;58(2):234-241.*.

7. Cereda E, Pedrolli C, Zagami A, et al. Body mass index and mortality in institutionalized elderly. *J Am Med Dir Assoc* 2011;12(3):174-178.

8. Kvamme JM, Holmen J, Wilsgaard T, et al. Body mass index and mortality in elderly men and women: the Tromso and HUNT studies. *J Epidemiol Community Health* 2012;66(7):611-617.

9. Socialstyrelsen. Näring för god vård och omsorg. En vägledning för att förebygga och behandla undernäring. (Swedish National Board of Health and Welfare. Nutrition for good health and social care). 2011. http://www.socialstyrelsen.se/publikationer2011/2011-9-2. Accessed September 3rd, 2013.

10. Vellas BJ GY, Garry PJ, Albarede JL, eds. *The Mini-Nutritonal Assessment: MNA.* 3rd ed. Paris: Serdi Publishing; 1997.

11. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol* 2009;66(3):336-342.

12. Kuo HK, Jones RN, Milberg WP, et al. Cognitive function in normal-weight, overweight, and obese older adults: an analysis of the Advanced Cognitive Training for Independent and Vital Elderly cohort. *J Am Geriatr Soc.* 2006;54(1):97-103.

13. Albanese E, Taylor C, Siervo M, et al. Dementia severity and weight loss: A comparison across eight cohorts. The 10/66 study. *Alzheimers Dement* 2013.

14. Buchman AS, Wilson RS, Bienias JL, et al. Change in body mass index and risk of incident Alzheimer disease. *Neurology* 2005;65(6):892-897.

15. Stewart R, Masaki K, Xue QL, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol* 2005;62(1):55-60.

16. Knopman DS, Edland SD, Cha RH, et al. Incident dementia in women is preceded by weight loss by at least a decade. *Neurology* 2007;69(8):739-746.

17. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at

midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* 2005;62(10):1556-1560.

18. Gustafson D, Rothenberg E, Blennow K, et al. An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Intern Med* 2003;163(13):1524-1528.

19. Faxen-Irving G, Basun H, Cederholm T. Nutritional and cognitive relationships and long-term mortality in patients with various dementia disorders. *Age Ageing* 2005;34(2):136-141.

20. Thies W, Bleiler L. 2013 Alzheimer's disease facts and figures. *Alzheimers Dement* 2013;9(2):208-245.

21. Wimo A, Religa D, Spångberg K, Edlund AK, Winblad B, Eriksdotter M. Costs of diagnosing dementia: results from SveDem, the Swedish Dementia Registry. *Int J Geriatr Psychiatry.* 2013;28(10):1039-1044.

22. Organization WH. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. In. Geneva: World Health Organization; 1992.

23. Religa D, Spangberg K, Wimo A, et al. Dementia diagnosis differs in men and women and depends on age and dementia severity: data from SveDem, the Swedish Dementia Quality Registry. *Dement Geriatr Cogn Disord* 2012;33(2-3):90-95.

24. Johnell K, Religa D, Eriksdotter M. Differences in Drug Therapy between Dementia Disorders in the Swedish Dementia Registry: A Nationwide Study of over 7,000 Patients. *Dement Geriatr Cogn Disord* 2013;35(5-6):239-248.

25. Schneeweiss S, Seeger JD, Maclure M, et al. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol* 2001;154(9):854-864.

26. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. *J Alzheimers Dis* 2006;9(3 Suppl):417-423.

27. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 2007;22(12):1689-1707; quiz 1837.

28. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry.* 1994;57(4):416-418.

29. Socialstyrelsen. Nationella riktlinjer för vård och omsorg vid demenssjukdom 2010-stöd för styrning och ledning. (Swedish National Board of Health and Welfare. National Guidelines for Care in Cases of Dementia 2010) http://www.socialstyrelsen.se. Accessed September 25th, 2013.

30. SveDem styrgruppen. Årsrapport SveDem 2011. (SveDem stirring committee. Yearly report on SveDem 2011). http://www.ucr.uu.se/svedem/index.php/om-svedem/arsrapporter. Updated November 28th, 2012. Accessed September 25th, 2013

31. Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* 2001;56(6):M366-372.

32. BMI classification. (Accessed at http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.)

33. Masters RK, Powers DA, Link BG. Obesity and US mortality risk over the adult life course. *Am J Epidemiol* 2013;177(5):431-442.

34. Kim JH, Choi SH, Lim S, et al. Sarcopenia and obesity: gender-different relationship with functional limitation in older persons. *J Korean Med Sci* 2013;28(7):1041-1047.

35. Friedmann JM, Elasy T, Jensen GL. The relationship between body mass index and self-reported functional limitation among older adults: a gender difference. *J Am Geriatr Soc.* 2001;49(4):398-403.

36. Landi F, Liperoti R, Fusco D, et al. Sarcopenia and mortality among older nursing home residents. *J Am Med Dir Assoc* 2012;13(2):121-126.

37. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc.* 2002;50(5):889-896.

38. Cameron AJ, Magliano DJ, Soderberg S. A systematic review of the impact of including both waist and hip circumference in risk models for cardiovascular diseases, diabetes and mortality. *Obes Rev* 2013;14(1):86-94.

39. Martin-Ponce E, Santolaria F, Aleman-Valls MR, et al. Factors involved in the paradox of reverse epidemiology. *Clin Nutr* 2010;29(4):501-506.

40. Dahl AK, Fauth EB, Ernsth-Bravell M, et al. Body mass index, change in body mass index, and survival in old and very old persons. *J Am Geriatr Soc.* 2013;61(4):512-518.

41. Luchsinger JAP, B. Tang M.X, Schupf, N. Mayeux, R. Body mass index, dementia and mortality in the elderly. *J Nutr Health Aging* 2008;12(2):127-131.

42. Masters RK, Reither EN, Powers DA, et al. The Impact of Obesity on US Mortality Levels: The Importance of Age and Cohort Factors in Population Estimates. *Am J Public Health* 2013.

43. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev* 2007;8(1):41-59.

44. Stevens J, Cai J, Pamuk ER, et al. The effect of age on the association between body-mass index and mortality. *N Engl J Med* 1998;338(1):1-7.

45. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, et al. Reverse epidemiology: a spurious hypothesis or a hardcore reality? *Blood Purif* 2005;23(1):57-63.

46. Landi F, Onder G, Gambassi G, et al. Body mass index and mortality among hospitalized patients. *Arch Intern Med* 2000;160(17):2641-2644.

47. Andersen KK, Olsen TS. Body Mass Index and Stroke: Overweight and Obesity Less Often Associated with Stroke Recurrence. *J Stroke Cerebrovasc Dis* 2013.

48. Guder G, Frantz S, Bauersachs J, et al. Reverse epidemiology in systolic and nonsystolic heart failure: cumulative prognostic benefit of classical cardiovascular risk factors. *Circ*

Heart Fail 2009;2(6):563-571.

49. Kopple JD. The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. *Am J Clin Nutr* 2005;81(6):1257-1266.

50. Colecraft E. HIV/AIDS: nutritional implications and impact on human development. *Proc Nutr Soc* 2008;67(1):109-113.

51. Pecoits-Filho R, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome -- the heart of the matter. *Nephrol Dial Transplant* 2002;17 Suppl 1128-31.

52. Liu Y, Coresh J, Eustace JA, et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2004;291(4):451-459.

53. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc* 2011;12(4):249-256.

54. Michaud M, Balardy L, Moulis G, et al. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc* 2013;14(12):877-882.

55. FASS. (Swedish Drug Index). http://www.fass.se/LIF/startpage?5. Accessed November 28th, 2013.

Figure 1.Title: Hazard of mortality per point change in BMI as obtained by Cox regression using linear splines.

Legend: BMI spline variables entered into Cox hazard regression. Results are adjusted by age (entered as a quadratic term), sex, Mini-Mental State Examination (MMSE), dementia diagnosis, and number of medication at the beginning of diagnostic work-up (all entered as categorical variables). 1a: split by gender. 1b: by age tertiles. Vertical axis on a logarithmic scale; represents HRs relative to the point of lowest mortality (at BMI 30). Results are fully adjusted as in table 4.

Table 1. Characteristics of study subjects

		N (%)	Dead N (%)	PYAR	Deaths /1000 PYAR
All		11398 (100.0)	3162 (27.7)	28190	112
Sex	Women	6734 (59.1)	1698 (25.2)	17080	99
	Men	4664 (40.9)	1464 (31.4)	11110	132
Age	<76	3630 (31.8)	556 (15.3)	9625	58
	76-83	396 (134.8)	1035 (26.1)	10042	103
	>83	3807 (33.4)	1571 (41.3)	8523	184
Mean (SD)		78.5 (7.9)			
Dementia diagnosis	AD	4092 (35.9)	793 (19.4)	10795	73
	Mixed	3076 (27.0)	940 (30.6)	7400	127
	VD	2124 (18.6)	771 (36.3)	4904	157
	LBD	331 (2.9)	111 (33.5)	807	138
	FTD	259 (2.3)	65 (25.1)	622	105
	PDD	173 (1.5)	47 (27.2)	413	114
	Unspecified	1103 (9.7)	367 (33.3)	2639	139
	Other	240 (2.1)	68 (28.3)	609	112
MMSE	≥25	3396 (29.8)	596 (17.6)	8916	67
	20-24	4193 (36.8)	1089 (26.0)	10476	104
	10-19	3080 (27.0)	1126 (36.6)	7245	155
	<10	269 (2.4)	115 (42.8)	580	198
	Not assessable	227 (2.0)	127 (55.9)	516	246
	Missing	233 (2.0)	109 (46.8)	448	243
Mean (SD)		21.4 (5.1)			
Number of medication before diagnosis					
	<2	1859 (16.3)	328 (17.6)	4945	66
	2-5	5153 (45.2)	1299 (25.2)	13079	99
	6-9	3157 (27.7)	996 (31.5)	7526	132
	>10	987 (8.7)	436 (44.2)	2063	211
	Missing	262 (2.3)	103 (39.3)	577	179
Mean (SD)		4.8 (3.3)			

Table 1: characteristics of study subjects**.** Number of patients (N) and percentages, or means and standard deviations (SD) are given as appropriate. PYAR: person-years at risk. Age categories correspond to the tertile distribution of age in the sample. MMSE categories result from the tertile distribution of MMSE in the sample (cut points at 19 and 25) with a further subdivision of the lowest MMSE category so as not to group patients with very different cognitive performance, plus another category for those in which MMSE was not assessable. Number of medication corresponds to the sum of all pharmacological treatments, as defined by the official Swedish Drug Index[55], that the patient was regularly taking at the time of diagnosis.

Table 2. Characteristics of subjects and mortality in each BMI category

	N (%)	Women N (%)	Age mean (SD)	MMSE mean (SD)	No. of medication mean (SD)	Dead N (%)	PYAR	Deaths /PYAR
Global	11398 (100)	6734 (59.1)	78.5 (7.9)	21.4 (5.1)	4.8 (3.3)	3162 (27.7)	28190	112
BMI mean (SD)			24.5 (4.3)					
BMI <18.5	631 (5.5)	517 (81.9)	79.9 (8.1)	19.8 (5.4)	4.5 (3.4)	270 (42.8)	1358	199
BMI 18.5-22.9	3740 (32.8)	2405 (64.2)	79.4 (7.9)	21.1 (5.0)	4.4 (3.2)	1182 (31.6)	9025	131
BMI 23-24.9	2367 (20.8)	1284 (54.2)	78.5 (7.9)	21.8 (4.9)	4.6 (3.1)	604 (25.5)	5927	102
BMI 25-29.9	3492 (30.6)	1839 (52.7)	77.9 (7.9)	21.6 (5.1)	4.9 (3.2)	846 (24.2)	8859	96
BMI≥30	1168 (10.3)	689 (59.0)	76.3 (7.9)	21.7 (5.0)	5.8 (3.5)	260 (22.3)	3021	86

Table 2: characteristics of subjects in each body-mass index (BMI) category. N: number of patients; SD: standard deviation; MMSE: Mini-Mental State Examination; PYAR: person-years at risk. No: number. Number of medication corresponds to the sum of all pharmacological treatments, as defined by the official Swedish Drug Index[55], that the patient was regularly taking at the time of diagnosis.

Table 3	Adjusted HR for death by BMI category								
	BMI<18.5		BMI 18.5-22.9	BMI 23-24.9		BMI 25-29.9		BMI over 30	
	HR	95% CI		HR	95% CI	HR	95% CI	HR	95% CI
All	1.60	1.39-1.84		0.81	0.73-0.89	0.73	0.66-0.85	**0.68**	**0.59-0.78**
Grouped by sex									
Women	1.62	1.38-1.89		0.81	0.70-0.93	**0.75**	**0.61-0.79**	0.77	0.65-0.93
Men	1.62	1.23-2.14	Ref	0.80	0.69-0.93	0.69	0.61-0.79	**0.58**	**0.47-0.72**
Grouped by age									
Under 76	1.42	1.00-1.99		0.73	0.57-0.93	0.62	0.50-0.77	**0.59**	**0.44-0.78**
76 to 83	1.58	1.23-2.03		0.75	0.63-0.89	0.71	0.61-0.83	**0.62**	**0.49-0.78**
Over 83	1.66	1.38-2.00		0.89	0.77-1.02	**0.78**	**0.69-0.89**	0.79	0.63-0.98

Table 3. Hazard ratios (HR) for death by BMI group, adjusted for results from Mini-Mental State Examination (MMSE), dementia diagnosis and number of medication before diagnosis. MMSE score was classified as not assessable, severe (0-9), moderate (10-19), mild (20-24), and slight impairment (25 and over). Dementia diagnosis was entered as eight diagnostic categories (Alzheimer's dementia [AD], Vascular dementia [VaD], mixed AD and VaD, Lewy Body dementia, Frontotemporal dementia, Parkinson's disease with dementia, unspecified dementia and other dementia diagnoses). Number of medication corresponds to the sum of all pharmacological treatments, as defined by the official Swedish Drug Index[55], that the patient was regularly taking at the time of diagnosis, and was categorized as 0-1, 2-5, 6-9, and 10 or more habitual drugs at time of diagnostic workup. Results for all patients, women and men are additionally adjusted with a quadratic term for age. Results for age categories are additionally adjusted for sex.

The slim group (BMI 18.5-22.9) serves as reference category. 95% confidence intervals (CI) and p values are given. BMI categories with HR for lowest mortality are highlighted.

Table 4. Adjusted HR obtained from BMI spline analyses.

	All			Women			Men		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
BMI<18.5	0.89	0.82-0.96	0.003	0.83	0.76-0.91	<0.001	1.08	0.89-1.29	0.426
BMI 18.5-22	0.89	0.85-0.93	<0.001	0.92	0.87-0.97	0.004	0.82	0.76-0.89	<0.001
BMI 22-24.9	0.95	0.91-0.99	0.027	0.94	0.88-1.00	0.050	0.97	0.91-1.03	0.357
BMI 25-29.9	0.97	0.94-0.99	0.037	0.99	0.95-1.04	0.667	0.94	0.90-0.99	0.014
BMI ≥30	1.03	0.99-1.06	0.144	1.03	0.99-1.07	0.205	1.01	0.95-1.07	0.804

Table 4. Spline variables entered into Cox hazard regression for the whole database, women and men. Hazard ratios (HR) correspond to mortality risk per point increase in BMI within the specified BMI range. 95% confidence intervals (CI) and p values are given. Results are adjusted by age (entered as a quadratic term), sex, Mini-Mental State Examination (MMSE), dementia diagnosis, and number of medication at the beginning of diagnostic work-up (all entered as categorical variables).